

b. Fetal Responses

Litter size: no statistically significant difference was seen between treated and controls
 Viability: no statistically significant difference was seen between treated and controls
 Mean fetal weight: ↓ in groups 2 and 3 compared to their matching controls
 Fetal examinations: - no statistically significant differences were seen in the size of the fetuses
 - no significant external or visceral malformations
 a few isolated abnormalities and anatomical variations were seen with comparable frequency in all the groups
 - ossification delay of skeletons in Group 2; this was explained by the sponsor to be due to maternal toxicity and not to direct embryotoxicity; this is possible but not proven

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

Conducted by sponsor at TRISA in France as a GLP study (French GLP) and with signed and dated QA statement. The study was completed by March 15, 1994. At the dose level studied, oxaliplatin induced a dose related decrease in food consumption in pregnant rabbits, but induced no abortions or embryotoxic or teratogenic effects in fetuses.

species: New Zealand Rabbits (15/mated ♀s/group)
 age; weight: adult age; mean body weight = 3.06 ± 0.32 kg
 drug: Oxaliplatin (batch 91-012)
 vehicle: 5% isotonic sterile glucose solution
 dosage: oxaliplatin: 0, 0.2, 0.4 and 0.8 mg/kg/day (0, 3, 6 and 12 mg/m²/day)
 cisplatin: 0.2 mg/kg/day
 route: I.V. (1 ml/kg) via caudal veins under light ether anesthesia
 duration: daily × 13, during gestation days 6-18

Observations

Maternal Responses

Clinical signs and mortality	twice daily except weekends and holidays
Body weights	daily during the treatment period
Food and water intake	recorded daily by visual inspection
Hysterectomy	at D28 of gestation
Gross Pathology	at necropsy at D28 of gestation

Fetal responses

Viability, litter size, number and distribution of implantations, early and late resorptions, dead fetuses, and gross abnormalities of the organs

Results

a. Maternal Response

Clinical signs: no oxaliplatin-related clinical or behavioral abnormalities
 67% of animals in cisplatin treated group had poor tolerance at the injection site (from gestation D12 on)
 Mortality: no oxaliplatin-related mortality
 1/15 died on gestation day 26-27 in cisplatin treated group
 Body weight: no significant change

Food intake: seems to have a dose-related ↓ in food intake in oxaliplatin-treated animals

	Control	LD	MD	HD
No. of animals with ↓ food intake	2/12	4/14	7/14	5/14
Extent of ↓ (%)	42-55	58-70	36-72	45-92
Duration (days)	1-7	11-14	6-16	5-10

↓ food intake in 14/14 cisplatin-treated animals:
 4/14 had a mean ↓ by 51% over 6 days
 10/14 had a mean ↓ by 75% between D11-20

Hysterectomy: the percentage of pre-implantation loss is equivalent among the groups
 the percentage of post-implantation loss is markedly higher in group 5 (cisplatin)
 2 dead fetuses were seen in oxaliplatin MD group
 21 dead fetuses were seen in cisplatin group

Hysterectomy Data Summary:

Groups	Control	LD	MD	HD	Cisplatin
Dosage (mg/kg/day)	0	0.2	0.4	0.8	0.2
Parents					
♀s with sperm	15/15	15/15	15/15	15/15	15/15
Evaluated pregnant ♀s	12	14	14	14	14
Litters (F1) ^a					
Corpora lutea	9.8	9.2	9.8	9.9	9.3
Implantations	9.3	8.6	9.4	9.3	9.0
Live fetuses	7.8	7.8	8.1	7.9	7.0 ^a
Dead fetuses	0.0	0.0	0.1	0.0	0.9 ^b
Resorptions	2.0	0.8	1.2	1.4	2.0
Weight of fetuses (g)	37.9	33.7	32.9	34.7	30.7
Sex ratios of fetuses (♂/♀)	0.95	0.91	0.85	1.14	1.08

^a 3 ♀s in this group did not have any live fetuses, 7.0 is the mean of 11 females; ^b 1 ♀ died at the end of gestation; 0.9 is the mean of 13 live ♀s

Overall Reproductive Toxicity Summary

Assessment of Concern for Human Reproductive and Developmental Toxicities of Oxaliplatin

Factors for Assessment	Fertility & Fecundity	Developmental Mortality	Alteration to growth
Signal Strength I	+1	+1	+1
Cross-species Concordance	↑	-	-
Multiplicity of effects	-	↑	↑
Adverse Effects as function of time	↑	↑	-
Signal Strength II	0	0	0
Maternal Toxicity	-	-	-
Dose-Response	-	-	-
Rare Events	-	-	-
Pharmacodynamics	+1	+1	+1
Therapeutic Index	-	-	-
Similarity Pharmacologic & Toxic mechanism	↑	↑	↑
Concordance between Test Species & Humans	+1	+1	+1
Metabolism	↑	↑	↑
General Toxicity	↑	↑	↑
Relative Exposures	+1	+1	+1
Class Alerts	+1	0	0
Total	+5	+4	+4

Consideration of the individual factors in the draft *Pregnancy Integration Tool* indicates that there is significant concern for adverse effect of oxaliplatin on three human reproductive and developmental endpoints: developmental mortality, fertility, and alteration to growth. The concerns for the three endpoints with positive signals are increased after considering pharmacodynamics, cross-species concordance, relative exposures, and class alert (fertility only). Adjustments to concerns for the factors Signal Strength I and II are described below with the overall assessments of each individual endpoint.

Factors applying equally to all positive endpoints

Pharmacodynamics. For pharmacodynamics, the toxicologic effects are a direct extension of the pharmacologic effect (DNA adduct formation). Concern is thus increased for all positive endpoints.

Concordance between Test Species & Humans. Concern is increased because biotransformation of oxaliplatin is non-enzymatic and is similar across species. However, no data was provided assessing the sensitivity to metabolites in humans. Thus in the absence of human data that would diminish the interspecies concordance, the metabolism data enhances concern within this factor. There is further enhanced concern because the overall toxicity profile is similar across the species. Myelosuppression, hepatotoxicity, and renal toxicity were noted in rats and dogs. Most of these toxicities were also noted in humans. Concern is thus increased for any positive endpoint due to the "interspecies concordance" factor.

Relative Exposures. As summarized in the PK&TK section, exposure to oxaliplatin in humans cannot be readily extrapolated because the AUC exposure in humans were measured for the total platinum (in plasma and purified ultrafiltrable fraction), while in animals PK parameters were measured with different analytical methods and different analytes. Assuming the human exposure (AUC₀₋₄₈ of PUF) measured by FAA truly reflected the oxaliplatin concentration, then, the AUC₀₋₄₈/Dose (mg/m²) ratio ($8.12 \mu\text{g}\cdot\text{h}/\text{ml} / 130 \text{ mg}/\text{m}^2 = 0.062$) was quite close to that for the dog (0.07-0.08 or 0.17, depending on the assay method). However, the developmental mortality was observed in rats at doses (6 - 12 mg/m²) where exposure to oxaliplatin would be much lower than in humans at the recommended dose (85 -125 mg/m²), an expected difference in exposure of ~10 fold. Thus, there will be an increase in the level of concern for all positive endpoints due to this factor.

Class Alert. The use of cisplatin in the chemotherapy of testicular tumors is frequently associated with decreased spermatogenesis and abnormal Leydig cell function. Sperm production has been observed to return to normal levels in 50 to 60% of treated men one to three years after chemotherapy is discontinued. Although fertility is apparently reduced, it is still possible for these patients to father children. Thus there is a class alert for adverse effects on human fertility for platinum drugs.

There are now two reports of women who received a complete course of chemotherapy, including cisplatin, for the successful control of neoplastic disease and subsequently had a normal pregnancy. In a case report involving fetal exposure to cisplatin between 20 and 30 weeks gestation and carboplatin between 31 and 36 weeks, adverse effects on fetal development were not detected. Based on the absence of reported adverse effects on human development for cisplatin and carboplatin, there is no class alert for oxaliplatin for endpoints other than fertility.

Reference

1. Fossa SD et al: Post-treatment fertility in patients with testicular cancer. *Br J Urol* 57:210-214, 1985.
2. Meistrich ML et al: Recovery of sperm production after chemotherapy for osteosarcoma. *Cancer* 63:2115-2123, 1989.
3. Kreuser ED et al: Chronic gonadal toxicity in patients with testicular cancer after chemotherapy. *Eur J Cancer Clin Oncol* 22:289-294, 1986.
4. Hansen PV, Hansen SW: Gonadal function in men with testicular germ cell cancer: the influence of cisplatin-based chemotherapy. *Eur Urol* 23: 153-6, 1993.
5. Henderson CE, Elia G, Garfinkel D et al: Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary. *Gynecol Oncol* 1993; 49: 92-4.

Overall Assessment of Concern for Individual Positive Endpoints

Fertility and Fecundity:

A fertility study was conducted only in SD rats. No decrease in fertility index was observed although developmental mortality (complete resorption) was observed in HD group. Repeat dose toxicology studies in both rats and dogs revealed a gross atrophy of the testis and dose-related testicular hypoplasia in dogs. Concern is increased for Signal Strength I due to cross-species concordance and the adverse effect observed at multiple times (pre-mating gonadal effects and post-mating resorptions). There was a clear effect in the high dose groups in the rat fertility study, but the effects in the mid dose group was marginal. Although there was a maternal toxicity (\downarrow body weight observed in high dose group), whether the maternal toxicity is the cause of the observed adverse effect on fertility is uncertain. There is thus no adjustment to the concern based on dose response or maternal toxicity considerations under Signal Strength II. Although the rat study did not demonstrate a decrease in fertility index, the overall concern for adverse effects on human fertility from oxaliplatin exposure is significant (+5).

Developmental Mortality:

The embryo-killing effect of oxaliplatin was evident in rats but not rabbits. Although interspecies concordance was not evident (effects only seen in rats), the rabbits were not administered doses high enough to induce significant maternal toxicity (inadequate study). In addition to mortality, growth retardation was also seen. Early resorptions were seen in the Segment II study and dead fetuses were seen in the fertility study. There is thus an enhanced concern due to the adverse event as a function of time. Concern for Signal Strength I is thus increased. Under Signal Strength II, the dose response relationship can not be assessed because only a single dose was given in the Segment II study. Minimal maternal toxicity was seen (\downarrow b.w.) at the doses causing developmental toxicity, concern is thus not adjusted for this contributory element. Concerns is thus not adjusted (0) for the Signal Strength II factor. The overall concern for adverse effects on human development is significant (+4).

Alterations to Growth:

In the fertility study in SD rats, the body weight of the live fetuses decreased in HD group (D20 cesarean). In the Segment II study, the weight of fetuses was decreased and ossification was delayed when oxaliplatin was administered on D6-10. Concern for Signal Strength I is increased because there is multiplicity of effect. Data was not available to assess cross species concordance or adverse effects as a function of time. Concern for Signal Strength II is unchanged because dose response could not be assessed and, although minimal, some maternal toxicity (\downarrow b.w.) was seen at the doses causing growth

alterations. Data was not available to assess dose response. The overall concern for adverse effects on the growth of human fetuses is significant (+4).

Integrate Assessment of Negative finding

Dysmorphogenesis:

No external, visceral, or skeletal malformations was observed in rats and rabbits although the models and tests are all predictive for developmental toxicity. The rat study was adequate to detect dysmorphogenesis, however, complete fetal mortality occurred before any structural alterations were seen. For the rabbit, doses were not sufficient to cause either maternal toxicity or developmental mortality. This study is therefore not considered an adequate test of dysmorphogenic potential. No documented evidence of birth defect in humans administered cisplatin or carboplatin during pregnancy is available. Other effects were seen within the developmental toxicity category (mortality, growth alterations). Therefore, the animal studies suggest some minimal risk of oxaliplatin causing dysmorphogenesis in humans.

Endpoints not studied

Studies were not conducted to assess effects of oxaliplatin on parturition, lactation or functional toxicities. The label should state that no information is available to assess risks of these toxicities.

Overall Conclusion

Based on net values (≥ 4) obtained from the integrative assessment for assignment of concern, it appears there are significant degrees of concerns for developmental and reproductive toxicity for the endpoints of fertility, developmental mortality, and alterations to growth in humans from the exposure to oxaliplatin at the clinical dose proposed.

IX. Carcinogenicity

The carcinogenicity of oxaliplatin has not been studied in animals. However, based on the similar mechanism of action and genetic toxicity as cisplatin, which has sufficient evidence of carcinogenicity in animals and humans, oxaliplatin should be presumed to be a trans-species carcinogen.

X. 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/m² by intravenous infusion in non-sedated dogs. (Vol.1.22, p109)
 DIV0673 Cardiac toxicity study of 1670 RB in rats: comparison with 1571RB. (Vol. 1.22.p88)
 DIV0674 Study of the effects on the electrocardiogram after a single 150 mg/m² 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/m² 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)

Summary of Special Toxicity Studies

Several special toxicity studies were conducted to investigate specific target organ toxicities of oxaliplatin. These studies included studies on local tolerance, cardiac toxicity, nephrotoxicity and myelotoxicity. Some of these studies included other drugs, *e.g.*, cisplatin and/or carboplatin, as comparison agents for the target organ toxicity.

Oxaliplatin produced ventricular fibrillation and death in dogs that received single dosages ≥ 7.5 mg/kg (150 mg/m²). The hearts of dogs that died were 'unusually firm' but were histologically normal [DIV0626 and DIV0627]. Oxaliplatin-induced cardiac toxicity was not detected in special cardiac toxicity studies conducted in rats or monkeys (one study in each species) suggesting that either the dog is more sensitive than other species or that the phenomenon of oxaliplatin-related cardiotoxicity is species specific. Results of the specialized nephrotoxicity studies in rat demonstrated that oxaliplatin produces nephrotoxicity. Oxaliplatin has a lower potential to produce myelosuppression than carboplatin but to a similar extent as cisplatin. Oxaliplatin is neurotoxic, affecting the morphometry of neuronal cells *in vivo*. The overall summary for the special toxicology studies are summarized in the following table.

APPEARS THIS WAY
ON ORIGINAL

Studies Species (Animal #s)	Evaluation	Treatment	Major Findings	Study #s
Local Tolerance				
Rat (302)	Local tolerance at the injection sites	i.v.	No finding	TXA1429, DIV0679, TXC1025, FER0311
Rabbit (73)		i.v.	No finding	TER0308
Dog (36)		i.v.	No finding	TXC1026, DIV0669
Rabbit (3)	Irritation to the skin and eye	Topical application of solid oxaliplatin	Non-irritating to the skin and moderately irritating to the eye	TIP0079
Cardiac Toxicity				
Dog (3)	EKG and kalemia	Single i.v dose, 200 mg/m ²	Deaths by ventricular fibrillation Slight ↓ in blood potassium level	CVR0147
Dog (3)	EKG and kalemia	Single i.v dose, 150 mg/m ²	Deaths by ventricular fibrillation Slight ↓ in blood potassium level	DIV0674
Dog (1)	EKG	Single i.v dose, 200 mg/m ²	Death and ventricular fibrillation, vomiting	TXA0432
Dog (10)	Clinical signs, cardiovascular data and pathology	Single i.v. 0, 150 and 200 mg/m ²	200 mg/m ² was lethal (2/4 dogs), death due to ventricular fibrillation; no histologic finding in the heart	DIV0627
Rat (32)	Heart weight, Values of CK, α- HBDH/LDH	i.p. 66-84 mg/m ²	No significant cardiotoxicity was observed	DIV0673
Monkey (6)	Clinical signs EKG	1.5-h i.v. 70, 150 and 200 mg/m ²	No abnormalities at 3, 5 and 7 hrs for MD and HD	DIV0677
Nephrotoxicity				
Rat (24 ♂)	Urine level of γ-glutamyl transpeptidase, Creatinine, Leucine aminopeptidase and N-acetyl-β-D- glucosaminidase	Slow i.v. 40 mg/m ²	At equ. Platinum doses, cisplatin was much more nephrotoxic; oxaliplatin exhibited similar nephrotoxicity as carboplatin	DIV0678
Rat (32)	Clinical signs, organ weights and histopathology	i.v. at 0, 9, 18, and 36 mg/m ²	Dose-dependent mild to severe degeneration and/or necrosis of proximal tubule epithelium in the external zonal cortical zone in all three treatment groups	DIV0679
Myelotoxicity				
<i>In vitro</i> (human bone marrow stem cells)	CFU-G/M By 12-14 days	5 - 200 μM; 1 hr treatment	Oxaliplatin had less bone marrow suppressive potential than carboplatin	DIV0604
Neurotoxicity				
Rats (64)	Morphometric	i.p. 24 mg/m ² , 2qwk for 4.5 wks	Significant ↓ in neuronal cell and nuclear area in oxaliplatin and ormaplatin-treated rats; ↓ in large neuronal cell bodies	Holmes et al, 1998

Recommendations: The pharmacology/toxicology data submitted supports approval of Eloxatin for the treatment of advanced colorectal cancer in combination with 5-FU-based therapy with revisions to the labeling as noted in a separate review.

Division of Oncology Drug Products, HFD-150

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

NDA Labeling Review (Review #2)

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, I-OHP, NSC-266046, NSC-271670, JM-83, PR 54780, 1670 RB7

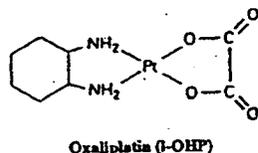
Trade Name: Eloxatin® for Injection (Eloxatine®, Dacplat®)

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



Molecular Formula/ Weight: C₈H₁₄N₂O₄Pt / 397.3

Related INDs/NDAs/DMFs: IND

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)		Function
Oxaliplatin	50 mg Product 50.00	100 mg Product 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/m² every two weeks or 125 mg/m² 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 See the Separate NDA Review #1

Note: Portions of this review were excerpted directly from the sponsor's submission

Labeling Comments

The oxaliplatin package insert submitted by the sponsor for NDA 21-063 should be changed as follows:

DESCRIPTION

CLINICAL PHARMACOLOGY

Mechanism of Action

Draft

1 pages redacted from this section of
the approval package consisted of draft labeling

APR 16 1993

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
ORIGINAL

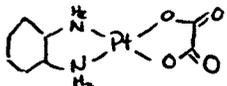
IND —

Reviewer: Wendelyn J. Schmidt, Ph.D.
Received by reviewer: 3/3/93
Completed: 4/13/93

Sponsor: Axion Pharmaceuticals, Inc.

Drug Name: Oxaliplatin (API-395)

Chemical Name: oxalato(trans-1-1,2-diaminocyclohexane)platinum(II)

Structure:  mw 397.3

Indication: Antineoplastic agent

Related Drugs and IND/NDA's: none

Information to be relayed to Sponsor: N

Proposed Clinical Study: a single dose schedule intensification trial from 130 to 200 mg/m² once every 3 weeks, as well as a weekly and every 14 day schedule for dose escalation (14 day schedule escalates from 90 mg/m² to 150 mg/m²), weekly schedule escalates from 65 mg/m² to 110 mg/m²).

Dosage Forms and Route of Administration: lyophilized product with lactose, reconstituted in sterile water and diluted in D5W for i.v. administration.

Studies Received:

I. Pharmacology

1. Mathe et al., Antitumor activity of 1-OHP in mice. *Cancer Letters* 1985; 27:135-143.
2. Mathe et al., Oxalato-platinum of 1-OHP, a third generation platinum complex: an experimental and clinical appraisal and preliminary comparison with cis-platinum and carboplatin. *Biomed. Pharmacother.* 1989; 43:237-250.
3. Kidani et al., Examination of antitumor activities of platinum complexes of 1,2-diaminocyclohexane isomers and their related complexes. *Gann* 1976; 67: 921-922.
Kidani et al., Antitumor activity of 1,2-diaminocyclohexane-platinum complexes against sarcoma-180 ascites form. *J. Med. Chem.* 1978; 21: 1315-1318.
Kidani et al., Antitumor activity of platinum (II) complexes of 1,2-diaminocyclohexane isomers. *Gann* 1980; 71: 637-643.
Noji et al., 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.* 1981; 24: 508-515.
4. Pendyala et al., In vitro cytotoxicity studies of oxaliplatin in human tumor cell lines. *Proc. AACR* 1991; 32:410 (abstr.).
Pendyala and Creaven, In vitro comparative cytotoxicity studies of oxaliplatin. *Debiopharm Int. rep.* 1990.
Pendyala. Personal communication, 1992.

5. Silvestro et al., Comparative effects of a new platinum analog (trans-1-diamine-cyclohexane oxalato platinum; L-OHP) with cDDP on various cells correlation with intracellular accumulation. Third Intl. Conf. Anticancer Res. 1990.
 6. Tashiro et al., Antitumor activity of a new platinum complex, oxalato (trans-1-1,2,-diaminocyclohexane)platinum(II): new experimental data. Biomed. Pharmacother. 1989; 43: 251-260.
 7. Vollano et al., Comparative antitumor activities on platinum(II) and platinum (IV) complexes containing 1,2-diaminocyclohexane. J. Med. Chem. 1987; 30: 716-719.
- II. Pharmacokinetics:
1. Boughattas et al., Report on the pharmacokinetics of L-OHP in mice. Debiopharm Int. Rep. 1991.
 2. Boughattas et al., Report on the distribution of platinum in the tissues of mice following the administration of L-OHP: comparison with cisplatin and carboplatin. Debiopharm Int. Rep. 1991.
 3. Los et al., The use of oxaliplatin versus cisplatin in intraperitoneal chemotherapy in cancers restricted to the peritoneal cavity in the rat. Cancer Letters 1990; 51: 109-117.
 4. Pendyala and Creaven, In vitro protein binding and red blood cell partitioning of oxaliplatin. RPCI rep. 1990.
 5. Pendyala and Creaven, In vitro biotransformation of oxaliplatin in plasma. RPCI rep. 1991.
 - ✓ 6. Peytavin, Comparative pharmacokinetics study of 3 platinum derivatives: cisplatin, carboplatin and oxaliplatin. Hopital Paul Brousse Int. Rep. 1988.
 - 13. Tapiero, Pharmacocinetique du trans-1-diamino-cyclohexane oxalato-platinum (l'OHP): etude preliminaire. Debiopharm int. rep.
 14. Vermorken et al., Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. Clin. Pharmacol. Ther. 1986; 39: 136-144.
- IV. Genotoxicology
1. Fournier et al., Oxaliplatin--Test of the bone marrow micronucleus in mice by the i.p. route. Rhone Poulenc Int. Rep. 200, 1988.
 2. Marzin, Assay of mutations at the TK locus in L5178Y mouse lymphoma cells by the microtitation technique (resistance to trifluorothymidine), oxaliplatin vs. cisplatin. Institut Pasteur de Lille, 1992.
 3. Marzin, Comparison of the activity of L-OHP (oxaliplatin) and cisplatin: a study of chromosomal abnormalities by metaphase analysis of human lymphocytes in culture. Institut Pasteur de Lille, 1992.
 4. Thybaud et al., Oxaliplatine (RP 54,7S0) in vitro mutagenicity test. Ames test. Rhone Poulenc Int. Rep. 176-E, 1988.

Studies previously reviewed:

Toxicology

Acute Toxicity:

1. Corrolier et al., Acute i.v. toxicity in the mouse. Study of lethality. Rhone-Poulenc rep. ST/CRV/TOX 196, 1989.
2. D'Alayer et al., Intravenous acute toxicity in the rat. T.R.I.S.A. Lab rep T922, 1989.
3. Godard, Acute toxicity of oxalato DACH-Pt(II) (Oxaliplatin) in mice and

rats: Comparison with 1571 RB. Lab. Roger Bellon Int. Rep. LRB 106/85, 1985.

4. Roquet and Godard, Oxalato-platinum complex of trans-1-diamino-cyclohexane 1-OHP=1670RB. Toxicity study in mice and rats. Laboratoire Roger Bellon Int. Rep. LRB 318/85, 1985.

5. Baudet, 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, 1992.

6. Baudet, 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, 1992.

7. D'Alayer et al., 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, 1990.

8. Roquet, Toxicological study of oxalato platinum in dog. Laboratoire Roger Bellon Int. Rep. LRB 320/85, 1985.

9. Plard et al., Preliminary toxicological study of 54 780 RP in dogs, administered i.v. in sequential treatment. Rhone Poulenc Int. Reo. 151, 1987.

10. D'Alayer et al., 9 week toxicity study in the dog comprising 3 i.v. perfusions at 3 week intervals. T.R.I.S.A Lab. rep. TP995, 1992.

11. D'Alayer et al., 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. T929, 1990.

12. Mathe et al., Repeated dose toxicology study of oxaliplatin or 1-OHP in baboons. Hopital Suisse de Paris Int. Rep. 1992.

Special Toxicity Studies:

1. Anjo et al., Notes on the cardiotoxicity of platinum complexes (except 1-OHP) in ultrastructural study. Biomed. and Pharmacother. 1989; 43: 265-266.

2. Cambar, Comparaison de la nephrotoxicite de trois derives du platine: approche experimentale in vivo. Universite de Bordeaux, 1990.

3. D'Alayer et al., Intravenous renal toxicity study in the rat. T.R.I.S.A. lab rep. T923, 1990.

4. Roquet and Godard. Cardiac toxicity of oxaliplatin in rats: Comparison with cisplatin. Laboratoire Roger Bellon Int. Rep., 1985.

5. Tapiero, Comparative analyses of the cardiotoxicity of anticancer medication: preliminary studies of trans-1-diaminocyclohexane oxalato platinum (1-OHP). Debiopharm Int. Rep. 1990.

Studies not reviewed:

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Note - Portions of this review were excerpted directly from the sponsor's submission.

I. Pharmacology

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

A series of murine tumors including L1210 and AkR leukemia, LGC lymphoma, B16 melanoma, M16 mammary adenocarcinoma, and Lewis lung carcinoma were exposed *in vivo* to i.v. or i.p. oxaliplatin and the effects noted and compared to those of cisplatin. The acute toxicity was also noted: the LD10 and LD50 (mg/kg) for the 2 compounds were identical. Oxaliplatin and cisplatin were equally effective against L1210 when administered i.v., but oxaliplatin was more effective i.p. than cisplatin (max %T/C at 6 mg/kg was 245 for oxaliplatin, 200 for cisplatin). Oxaliplatin was more effective than cisplatin on intracerebrally planted L1210 and LGC lymphoma, while cisplatin was more effective against AkR leukemia; activity was greatest at concentrations between 3 and 10 mg/kg. At 10 mg/kg, oxaliplatin did not affect urea or creatinine levels while cisplatin altered these parameters by a log factor. Neither compound was effective against the solid tumors tested.

2. Mathe et al., Oxalato-platinum of 1-OHP, a third generation platinum complex: an experimental and clinical appraisal and preliminary comparison with cis-platinum and carboplatinum. *Biomed. Pharmacother.* 1989; 43:237-250.

In this review paper, activity of oxaliplatin in solid tumors with treatment on day 1, 5, 9 was compared to cisplatin and carboplatin (results in table below). No cross-resistance was noted in a cisplatin-resistant L1210 cell line (although the respective activities against the parent cell line were not compared). In combination, the platinum compounds were slightly more effective against L1210 at half optimal doses, but with optimal doses, toxicity was evident. The paper also noted the diminished toxicity in mice, baboons and humans, as well as lack of mutagenicity.

Table III. Experimental antitumor activity [24, 41].

Reference screening center	Tumor graft criteria of evaluation	Treatment schedule	Daily dose range (mg/kg)	Optimal T/C (%)	Drugs compared	Daily dose range (mg/kg)	Optimal T/C (%)
24	MA 16-C	1, 5, 9	7.5-5.0	206	CDDP CBDCA	5 50	inactive inactive
41	B ₁₆ melanoma sc survival	1, 5, 9 i.p.	10-2.5	128	CDDP CBDCA	10-2.5 12.5-2.5	139 170
41	Lewis lung sc survival	q2d, d1-19 i.p.	5-1.25	159	CDDP CBDCA	2.5-1.25 60	184 245
41	C ₆ colon carcinoma survival	1, 5 i.p.	12.5-3.12	143	CDDP CBDCA	12.5-1.56 25	322

1-OHP = oxalato-platinum; CDDP = cisplatin; CBDCA = carboplatin.

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

Kidani et al., Antitumor activity of 1,2-diaminocyclohexane-platinum complexes against sarcoma-180 ascites form. *J. Med. Chem.* 1978; 21: 1315-1318.

Kidani et al., Antitumor activity of platinum (II) complexes of 1,2-diaminocyclohexane isomers. *Cann* 1980; 71: 637-643.

Noji et al., 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.* 1981; 24: 508-515.

The papers listed above are structure-activity type analyses of a series of platinum compounds with the DACH carrier ligand including 1-OHP. The results in the different cell lines with 1-OHP are summarized in the table below.

Cell Line	Dose (mg/kg)	Schedule	% T/C
P388	12.5	i.p., D1, D5	231
	6.25		188
	3.12		152
	1.56		125
S180	3	i.p. daily X 5	ascites PCV <10% t/c
L1210	12.5	i.p. D1, D5, D9	308

4. Pendyala et al., *In vitro* cytotoxicity studies of oxaliplatin in human tumor cell lines. *Proc. AACR* 1991; 32:410 (abstr.).

Pendyala and Creaven, *In vitro* comparative cytotoxicity studies of oxaliplatin. *Debiopharm Int. rep.* 1990.

Pendyala. Personal communication, 1992.

The human cell lines (bladder carcinoma RT4 and TCCSUP, ovarian carcinoma A2780, glioblastoma U373MG and U-87MG, colon carcinoma HT-29, and melanoma SK-MEL-2 and HT-144) were exposed to oxaliplatin for 48 hours in culture and the growth inhibition observed as a function of total protein. The results are summarized in the following table. Cisplatin and oxaliplatin were similarly effective against most cell lines tested, although the colon line was approximately 20 fold more sensitive to oxaliplatin than cisplatin. The OVCAR-3 cell line showed an IC50 of 25 μ M, approximately 5 fold less sensitive than cisplatin.

IC₅₀ (μ M) FOR THE 5 PLATINUM COMPLEXES

Pl. Complex	A2780 (OV)	TCC (BL)	RT4 (BL)	HT29 (CO)	U-87MG (CO)	U-373MG (CO)	SK-MEL-2 (ME)	HT-144 (ME)
CP	0.76	3.65	12.30	20.36	13.51	11.36	33.04	7.74
OB	19.00	64.00	216.36	339.74	201.60	233.90	343.42	110.00
IP	0.64	77.77	21.94	26.94	46.12	64.99	230.02	99.00
TP	0.17	10.44	7.03	2.05	4.49	4.03	34.67	4.34
OHP	0.17	15.04	11.10	0.97	19.49	2.93	20.55	7.05

5. Silvestro et al., Comparative effects of a new platinum analog (trans 1 diamine-cyclohexane oxalato platinum; L-OHP) with cDDP on various cells correlation with intracellular accumulation. Third Intl. Conf. Anticancer Res. 1990. (abstract).

The ID50 and intracellular accumulation of L-OHP and cisplatin were compared in a series of human tumor lines. The data is summarized in the table below. Constant and short (15-30 minute) exposures to drug were tested. Uptake was measured by atomic absorption spectroscopy after drug exposures of 14, 60 and 300 minutes; greater platinum levels at all time points with L-OHP was reflected in greater inter- and intra-strand DNA platinum linkage.

Cell line	ID50 (uM)		Pt uptake (pM) (1 hour)	
	cDDP	L-OHP	cDDP	L-OHP
HT29	0.62	0.7		
FLC leukemia (murine)	0.4	0.045		
MCF-7	4.2	0.3	238	372
K562 leukemia (human)	1.8	0.4		

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

Another structure-activity type paper discussing the activity of oxaliplatin versus the platinum(IV) analog in L1210 and B16 models. The results did not differ significantly from those already discussed.

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7. Tashiro et al., Antitumor activity of a new platinum complex, oxalato (trans 1-1,2,-diaminocyclohexane)platinum(II): new experimental data. Biomed. Pharmacother. 1989; 43: 251-260.

The activity of 1-OHP and cisplatin were compared in a number of tumor cell lines *in vivo*. The %T/C in the following table refers to either increased lifespan or tumor weight reduction. While 1-OHP was not cross resistant in L1210/DDP lines, cross resistance to DDP was demonstrated in the P3SS line. Oxaliplatin and cisplatin showed similar inhibition of DNA synthesis, but oxaliplatin showed greater inhibition of RNA synthesis. Oxaliplatin did not show any increase of revertants over control with or without S9 activation in TA100 and TA 98 S. Typhimurium lines.

Cell Line	Dose (mg/kg)	Schedule/ Route	%T/C	
			1-OHP	cDDP
L1210	6.25	i.p; d1,5,9	>253	249
	12.5	i.p. d1,5,9	>303	78
P3SS	3.12	i.p. d1,5,9	151	211
	6.25	i.p. d1,5,9	204	237
	12.5	i.p. d1,5,9	221	---
B16 (i.p.)	5	i.p. d1,5,9	129	210
	10	i.p. d1,5,9	200	toxic
B16 (s.c.)	5	i.p. d1,5,9	128 lifespan 37 weight	139 lifespan 10 weight
Lewis Lung	2.5	i.p. 10X every 2 days	145 lifespan 28 weight	184 lifespan 53 weight
Colon 26	12.5	i.p. d 1, 5	143	toxic
	6.25	i.p. d1, 5	125	322
Colon 38	10	i.p. d2, 9	153 lifespan 16 weight	153 lifespan 6 weight
M5076 fibrosarcoma s.c.	10	i.p. d 1,5,9	155 lifespan 1 weight	---
	5	i.p. d1,5,9	151 lifespan 9 weight	171 lifespan 16 weight
	5	i.p. d 1,5,9,14,18	187 lifespan 1 weight	162 lifespan 0 weight
M5076 i.p.	10	i.p. d1,5,9	358	---
	5	i.p. d1,5,9	303	211
L1210/DDP	6.25	i.p. d1,5,9	>726	107

Summary and Evaluation of Pharmacodynamics:

In hopes of finding a compound which circumvents the toxicities and increases the spectrum of activity of cisplatin (including abrogation of resistance), a series of second generation platinum complexes have been synthesized and tested. Oxaliplatin is one of these. The optically-active isomers of the diaminocyclohexane ligand are minimally cross-resistant in cisplatin resistant cell lines and less nephrotoxic. The oxalato substitution for the chloride ligands increases water solubility. The mechanism of action, binding to DNA is similar to that of cisplatin, although there are subtle differences in the preference for DNA bases and distortion of the DNA molecule following interaction.

In general, the potency of cisplatin and oxaliplatin are similar. Activity in cultured cell lines with oxaliplatin are in the 0.1-1 uM range for a series of human cell lines. Significant increases in lifespan were obtained in mice with 5-12.5 mg/kg, again, similar to the range necessary for cisplatin.

II. Pharmacokinetics:

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

No GLP/QA statement accompanied the data. Male B6D2F1 mice, 3 weeks old, were injected with 17 mg/kg l-OHP via the retro-orbital sinus. Blood samples were obtained at 5, 10, 20, and 35 minutes, 1, 2, 4, 6, and 24 hours after injection from the retro-orbital sinus. RBC, plasma (ultrafiltered and unfiltered) were analyzed for platinum by atomic absorption spectrophotometry.

Although the procedure states that oxaliplatin was diluted to "3.4 mg/L" in water, the dose and volume stated would necessitate a dilution of 3.4 mg/ml oxaliplatin in water. Free platinum (ultrafilterable) was undetectable after 1 hour. Platinum levels in RBC's and total plasma reached a constant level from 1 hour through 24 hours, with platinum levels in RBC's approximately 3 fold higher than in plasma. The AUC of free platinum was calculated to be 196 mg \cdot h/min. Carboplatin showed similarly low levels of platinum in RBC's, plasma and ultrafiltrate of plasma.

Time (min)	Platinum concentration (ng/l)		
	Free	Total	RBC
5	12.14	15.37	12.5
10	4.75	7.47	11.27
20	1.78	5.03	12.97
35	.91	3.43	10.17
60	.24	2	6.77
120		1.7	5.3

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2. 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.

No GLP or QA statements accompanied the data. B6D2F1 male mice (3 weeks old) were injected via the retro-orbital sinus with 17 mg/kg (LD50) of oxaliplatin dissolved in water. Equitoxic doses of cisplatin and carboplatin were also analyzed. Tissue samples were analyzed for platinum at 24 and 96 hours post-administration by atomic absorption spectrophotometry.

The largest concentrations of oxaliplatin were observed in the spleen kidney, g.i. tract, skin, heart, thymus, and lung. Lowest levels were noted in the brain. Levels of platinum in the kidney were 27% lower at 24 hours with oxaliplatin than with cisplatin. Levels of platinum at 96 hours after oxaliplatin administration were minimally changed in the spleen and liver, halved in the kidney, and quartered in the g.i. tract.

	Platinum concentration (ng/kg dry tissue)* 24 hours after administration		Platinum concentration (ng/kg dry tissue)* 24 hours after administration			Platinum concentration (ng/kg dry tissue)* 96 hours (1OHP, cisplatin) and 7 days (carboplatin) after administration				
	1OHP	Cisplatin	1OHP	Cisplatin	Carboplatin	1OHP (n=23)	Cisplatin (n=5)	Carboplatin (n=17)		
Skin	8.3 (2.7 - 9.6) (n=3)	7.6 (7.1 - 7.7) (n=3)	Spleen	39.4 (22.3 - 178.5) (n=23)	9.2 (3.6 - 12.6) (n=29)	29.2 (21.6 - 42.7) (n=17)	Spleen	55.6 (20.7 - 180.1)	8.4 (7.2 - 11.7)	52.8 (20.6 - 95.4)
Heart	7.9 (6.0 - 9.9) (n=4)	3.3 (2.9 - 3.7) (n=3)	Kidney	14.9 (2.8 - 24.6) (n=21)	20.5 (15.9 - 31.4) (n=18)	27.8 (22.9 - 28.9) (n=17)	Kidney	7.7 (0.4 - 19.2)	12.3 (7.3 - 18.5)	15.9 (12.2 - 46.2)
Thymus	7.8 (1.9 - 12.8) (n=4)	6.1 (2.4 - 4.9) (n=3)	Colon	9.3 (1.8 - 21.8) (n=21)	3.8 (2.3 - 5.4) (n=9)	17.3 (4.1 - 29.7) (n=17)	Colon	2.4 (0.9 - 12.0)	3.3 (1.9 - 4.6)	3.6 (1.5 - 5.6)
Lung	7.5 (5.6 - 11.0) (n=4)	4.7 (4.4 - 5.3) (n=3)	Liver	6.4 (2.8 - 15.8) (n=22)	12.6 (8.7 - 14.3) (n=9)	19.8 (11.2 - 20.4) (n=17)	Liver	7.1 (3.3 - 12.6)	14.8 (9.7 - 18.6)	21.4 (15.8 - 26.2)
Stomach	4.3 (3.8 - 5.3) (n=4)	2.9 (2.0 - 3.4) (n=3)	Dundenum	8.5 (2.6 - 41.7) (n=21)	5.1 (3.8 - 6.5) (n=18)	9.2 (7.9 - 11.8) (n=17)	Dundenum	1.8 (0.2 - 3.7)	1.7 (1.1 - 2.2)	2.8 (1.1 - 5.3)
Intestine	3.3 (2.7 - 4.4) (n=3)	2.0 (1.4 - 2.4) (n=3)	Jejunum	5.4 (0.1 - 12.9) (n=22)	4.2 (1.2 - 5.2) (n=9)	7.5 (4.8 - 11.6) (n=17)	Jejunum	1.3 (0.3 - 2.7)	1.5 (0.4 - 2.6)	2.2 (1.0 - 4.7)
Adrenals	3.4 (2.8 - 5.1) (n=4)	3.1 (2.8 - 4.2) (n=3)								
Brain	3.3 (2.8 - 4.1) (n=3)	2.5 (2.4 - 2.5) (n=3)								
Spleen	2.8 (1.6 - 4.4) (n=4)	2.8 (1.9 - 2.1) (n=3)								
Testis	1.3 (0.9 - 2.1) (n=12)	1.6 (1.2 - 2.2) (n=12)								
Uterus	0.6 (0.3 - 0.7) (n=4)	0.7 (0.6 - 0.7) (n=3)								
Carboplatin	0.5 (0.3 - 0.8) (n=4)	0.7 (0.6 - 1.1) (n=3)								

*Median (IQR)

*Median (IQR)

*Median (IQR)

3. Los et al., The use of oxaliplatin versus cisplatin in intraperitoneal chemotherapy in cancers restricted to the peritoneal cavity in the rat. Cancer Letters 1990; 51: 109-117.

Rats bearing the CC531 peritoneal tumors (multiple nodules on the diaphragm, peritoneum, mesothelium progressing to ascites) were treated 28 days after tumor injection ip or i.v. with equimolar concentrations of 1-OHP or cisplatin (6.6 and 5 mg/kg respectively). Tumor response, platinum uptake into tumor and pharmacokinetics were investigated.

Tissue distribution of oxaliplatin was similar to cisplatin in the kidney liver and intestines, but approximately doubled in spleen and lung with oxaliplatin. However, when tissue/plasma ratios were compared, less oxaliplatin than cisplatin was noted in all tissues but the gi tract and lungs. Concentrations of platinum in tumor were similar with cisplatin and oxaliplatin and increased linearly with dose. Distribution of platinum with oxaliplatin treatment within the tumor (periphery versus center) did not differ significantly (large error bars); cisplatin did show a trend toward less diffusion toward the center of the tumor. The AUC of both free and total platinum following i.p. administration of oxaliplatin was greater than that of cisplatin, although the half-lives did not differ to a statistically significant degree (240 vs. 180 minutes for total platinum in oxaliplatin and cisplatin respectively).

Table 5. Pharmacokinetic data in plasma and peritoneal cavity after i.p. treatment with equimolar concentrations 1-OHP and cDDP.

Parameter	1-OHP		cDDP	
	Total Pt	Free Pt	Total Pt	Free Pt
AUC _{0-24h} (µM·h)	315.0 ± 145	95.0 ± 15	98.0 ± 14	22.0 ± 7
T _{1/2} (min)	180.0 ± 90	90.0 ± 8.6	40.0 ± 8.6	40.0 ± 10
C ₀ (µM)	14.5 ± 3.1	10.9 ± 5.5	17.0 ± 2.6	11.0 ± 1.7
Tl/2 _{plasma} (120-1440min)	1422.0 ± 120	507.0 ± 65	658.0 ± 42	194.0 ± 25
AUC _{0-24h} (peritoneal cavity)	816.0 ± 42	565.0 ± 37	481.0 ± 110	338.0 ± 38
Tl/2 _{peritoneal} (60-1440min)	241.0 ± 45	230.0 ± 52	180.0 ± 62	150.0 ± 43

p.cavity = peritoneal cavity.

AUC = Area under the concentration x time curve (µM·h)

Results were obtained from at least four concentration x time curves for each drug.

4. Pendyala and Creaven, In vitro protein binding and red blood cell partitioning of oxaliplatin. RPCI rep. 1990.

Protein binding of oxaliplatin was measured in human plasma at varied concentrations for up to 2 days at 37° C and subjecting samples to ultrafiltration. Partitioning of oxaliplatin between RBC's and plasma was determined with incubation with whole blood, repartitioning from RBC's to plasma was determined following a 2 hour incubation with whole blood and resuspension for up to 4 hours in untreated plasma. Platinum levels were determined by atomic absorption.

Oxaliplatin was 85-88% protein bound independent of initial incubation concentration within 5 hours. The half-life for disappearance of free platinum was approximately 1.7 hours, which is similar to that seen with cisplatin and tetraplatin. Between 25 and 50% of the platinum concentration in whole blood was associated with the RBC and did not exchange into plasma over time.

5. Pendyala and Creaven, In vitro biotransformation of oxaliplatin in plasma. RPCI rep. 1991.

Oxaliplatin was incubated with plasma at an initial concentration of 50 µg/ml for up to 4 hours. Free (ultrafilterable) platinum was analyzed by HPLC and atomic absorption. Parent compound was no longer detectable at 2 hours. A new peak began to appear by 1 hour, which co-eluted with DACH-Pt-dichloro species. Several other unknown peaks were present by 2 hours and 4 hours.

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

The paper reviewed both the preclinical and clinical pharmacokinetics in comparison with cisplatin and carboplatin. All three platinum compounds fit a multi-compartment elimination model. The authors stated that terminal phase calculations are difficult due to the rapid disappearance of free platinum; excretion of platinum in the urine is as parent drug.

Summary and Evaluation of Pharmacokinetics:

Oxaliplatin, when administered i.v. or i.p. is extensively protein bound (approximately 85% of the administered dose), but only the ultrafiltrable ("free") fraction is active. The platinum also distributed into the RBC. In saline solutions, including plasma, oxaliplatin is converted to the less soluble DACH-Pt-Cl₂ within 2 hours. The terminal half-life of free platinum in mouse was less than 10 minutes, while the range in humans was not determined.

AUC of total platinum by the i.v. route in mouse was 196 mg•hr/l (493 uM•hr) with a dose of 17 mg/kg (51 mg/m²), in rat with i.p. administration of 6.6 mg/kg (40 mg/m²) AUC was 516 uM•hr, in humans by i.v. with 80-100 mg/m² AUC was 749 uM•hr. In other words, the AUC when normalized to dose on a mg/m² basis, was approximately twice as high in the rat than in human or mouse by the i.v. route. In humans, i.v. and i.p. administration produced AUC's and half-lives that were essentially identical. When compared to cisplatin by the i.p. route in the rat, oxaliplatin led to platinum AUC levels approximately twice those of cisplatin.

The majority of platinum in the mouse was seen in the spleen, kidney, colon, liver and gi tract. The greater concentration of oxaliplatin in spleen as compared to cisplatin or carboplatin could be associated with the increased partitioning of oxaliplatin into the RBC's; lower concentrations of 1-OHP in kidney and liver as compared to the other two platinum compounds correlates with the lower toxicities in these organs. With the exception of gi tract, concentrations of platinum in the organs remained relatively constant over 96 hours. In culture, cellular uptake was greater with oxaliplatin than with equimolar concentrations of cisplatin, leading to greater cross-linkage of DNA.

Elimination in the human was via the kidney; approximately 40% of the dose was excreted in the urine by 24 hours after administration.

HUMAN Route	T _{1/2} total Pt (hr)	Plasma clearance (ml/min)	Plasma C _{max} (μmol/L)	Plasma T _{max} (hr)	Areas under the curves (μmol/L hr)	Distribution volume (L)	MRT (hr)
I.V.	70.1±14.2	5.9±1.6	16.6±4.4	1	749.4±225.8	36.5±13.1	102.5±16.3
I.P.	68.8±28.5	6.4±4	8.9±1.3	4.65±1.9	857.4±416	30.6±6.5	100.7±38.4
Wilcoxon	NS*	NS*	S**	S**	NS*	NS*	NS*

DOSE 80 - 100 mg/m² i.v., 100 mg/patient i.p.

*NS = not significant, **S = significant

Table XII. Compared pharmacokinetic parameters of cisplatin, carboplatin and oxaliplatin [33]

Pharmacokinetic parameters	Cis-platin	Carbo-platin	Oxali-platin
T _{1/2} α total Pt (min.)	8.7-912	10.8-98	ND
T _{1/2} β total Pt (h.)	30.5-290.4	16.6-98	70.1
T _{1/2} α free Pt (min.)	2.7-78	5.7-125	ND
T _{1/2} β free Pt (min.)	25.9-226.8	102-436	ND
% Bound protein 4 h. post-infusion	90	24	ND
Excretion units/24 h. (% of dose admin.)			ND
Renal clearance of free Pt/FG count	0.38-3.62	0.7	ND
Plasma clearance of total Pt (ml/min/m ²)			5.9
Plasma clearance of free Pt (ml/min/m ²)	15.6-658	40-123	ND
Vol. (ml/m ²) total Pt	52.3-65.6	16.1-24	36.5
free Pt	21.2-50.5	17.3	
	23.6-81.9	16	
T _{1/2} free Pt in vitro (h)	1.5-3.7	30	
C _∞ total Pt plasma (μmol/l)			16.6
T _∞ total Pt (h)			1
AUC (μmol/l·h)			749.4
MRT (h)			102.5
Biliary excretion (% dose admin.)	< 0.06		

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IV. Genotoxicology

1. Fournier et al., Oxaliplatin - Test of the bone marrow micronucleus in mice by the i.p. route. Rhone Poulenc Int. Rep. 200, 1988.

The study was performed according to GLP and was accompanied by a QA statement. CD1 mice (5/sex/dose) were administered 4.11, 8.22 or 12.33 mg/kg oxaliplatin (batch BDN144) in water i.p. either once or twice at an interval of 24 hours and the marrow observed for micronuclei 24 hours after the last drug injection. Mitomycin (1 mg/kg) was used as a positive control.

All doses of oxaliplatin tested yielded a statistically significant increase in cells with micronuclei (over 35 fold greater than control, at least double the positive control). A second dose of oxaliplatin yielded too great a toxicity in the marrow to be able to evaluate micronuclei.

54 789 R.P. - Polychromatophil erythrocytes with micronuclei
Average values (per thousand polychromatophil erythrocytes)

Time (hours)	Control ^{a)}	54 789 R.P.			Mitomycin 1 mg/kg
		4.11 mg/kg	8.22 mg/kg	12.33 mg/kg	
24	mean ^{b)}	13	301**	669**	666**
	max ^{c)}	1.2	30.1	66.9	66.6
48	mean ^{b)}	13	782**	---	---
	max ^{c)}	1.3	78.2	---	---

a) Water for injectable preparations
b) Over 10,000 polychromatophil erythrocytes
c) Micronuclei not counted, cytotoxicity too high

2. Marzin, Assay of mutations at the TK locus in L5178Y mouse lymphoma cells by the microtitration technique (resistance to trifluorothymidine), oxaliplatin vs. cisplatin. Institut Pasteur de Lille, 1992.

The study was performed according to GLP and accompanied by QA statements. L5178Y TK⁺ cells were cultured with oxaliplatin or cisplatin in DMSO for 2 hours (with and without S9) at concentrations that did not decrease survival by more than 90% as compared to control. Actual concentrations tested were 0.5, 1, 2, 4, and 6 uM. Number of mutated colonies increased with increasing dose of both oxaliplatin and cisplatin independent of S9 activation. At 6 uM (with S9) and 8.3 uM (without S9), cisplatin increased mutation by 5.5 and 3.7 fold, while oxaliplatin increased mutation by 4.8 and 4.0 fold.

Cytotoxicity Test on L5178Y Mouse Lymphoma Cells Without Metabolic Activation

Product	Dose µM (µg/ml)	Negative Wells			PI(0)	Percent Survivors	Percent with respect to control substrate
		Plaque 1	Plaque 2	Total (of 122)			
Control Substrate	0	20	21	41	0.234	90.7	100
L-OMP	0.8 (0.33)	25	34	49	0.255	85.4	94.1
	1.7 (0.66)	25	25	50	0.260	84.1	92.7
	4.2 (1.65)	49	45	94	0.490	44.6	49.2
	8.3 (3.31)	91	91	182	0.948	3.3	3.7
	16.6 (6.62)	96	96	192	1.000	0.0	0.0
	33.3 (13.20)	96	96	192	1.000	0.0	0.0

Product	Dose µM (µg/ml)	Negative Wells			PI(0)	Percent Survivors	Percent with respect to control substrate
		Plaque 1	Plaque 2	Total (of 122)			
Control Substrate	0	20	21	41	0.234	90.7	100
cisplatin	0.8 (0.25)	28	26	54	0.281	79.3	87.4
	1.7 (0.5)	29	27	56	0.297	77.0	84.9
	4.2 (1.25)	39	35	74	0.490	44.6	49.2
	8.3 (2.5)	85	82	167	0.870	8.7	9.6
	16.6 (5)	95	94	189	0.964	1.0	1.1
	33.3 (10)	95	96	191	0.975	0.1	0.4

Mutation at TK Locus of L5178Y Mouse Lymphoma Cells With Metabolic Activation (Survival rate)

Assay No. 1
Time 0 after treatment

Product	Dose µM (µg/ml)	Negative Wells			PI(0)	Percent Survivors	Percent with respect to control substrate
		Plaque 1	Plaque 2	Total (of 122)			
Control Substrate	0	14	19	33	0.172	110.1	100
L-OMP	0.5 (0.2)	24	20	44	0.229	92.1	83.7
	1 (0.4)	27	31	58	0.302	74.8	68.0
	2 (0.8)	36	26	62	0.323	70.6	64.2
	4 (1.6)	63	59	122	0.635	28.3	25.8
	6 (2.4)	75	82	157	0.818	12.6	11.4
	MMS	25	31	27	58	0.302	74.8

Product	Dose µM (µg/ml)	Negative Wells			PI(0)	Percent Survivors	Percent with respect to control substrate
		Plaque 1	Plaque 2	Total (of 122)			
Control Substrate	0	14	19	33	0.172	110.1	100
cisplatin	0.5 (0.15)	19	16	35	0.182	106.4	94.7
	1 (0.3)	28	25	45	0.234	90.7	82.4
	2 (0.6)	34	32	66	0.344	66.7	60.6
	4 (1.2)	73	82	155	0.807	13.4	12.2
	6 (1.8)	75	80	152	0.848	3.3	3.0
	MMS	25	31	27	58	0.302	74.8

3. Marzin, Comparison of the activity of 1-OHP (oxaliplatin) and cisplatin: a study of chromosomal abnormalities by metaphase analysis of human lymphocytes in culture. Institut Pasteur de Lille, 1992.

GLP and QA statements were included. Human lymphocytes were cultured with (1 hour) and without S9 fraction (24 hours), and oxaliplatin or cisplatin at 2, 4, 8, 16, and 32 uM or 0.5, 1, 2, 4, and 8 uM respectively. Positive controls were mitomycin C and cyclophosphamide. Metaphase chromosome spreads were analyzed 24 hours after the start of treatment.

With oxaliplatin without metabolic activation, gaps/cell did not alter significantly, but breaks/cell increased dose dependently to a maximum of approximately 12 fold over control (although the positive control showed an increase of 45 fold. Total cells with all aberrations increased 4.5 fold in positive controls, 4 fold at oxaliplatin at 4 uM (increases of 8 fold seen with equimolar concentration of cisplatin. In the lymphocytes with metabolic activation, aberrant metaphases increased approximately 3 fold in both positive controls and 1-OHP-treated cells at 32 uM (cisplatin increased aberrant metaphases by 24 fold).

ANALYSE DE METAPHASES IN VITRO SUR LYMPHOCYTES HUMAINS
RECHERCHE D'ACTIVITE GENOTOXIQUE EN PRESENCE D'ACTIVATION METABOLIQUE

PRODUITS	DOSES µM	GAPS PAR CELLULE	BREAKS PAR CELLULE	NOMBRE DE CELLULES ANORMALES/ NOMBRE DE CELLULES OBSERVEES	TOTAL DES ANOMALIES	NOMBRE TOTAL DE CELLULES PORTANT DES ANOMALIES DE STRUCTURE	
						EXCLUANT LES CELLULES A GAPS SEULS	INCLUANT LES CELLULES A GAPS SEULS
TENUON	0	0,04	0,045	0	0	0	0
	1	0,126	0,222	0	0	0	0
	2	0,06	1,00	0	0	0	0
	4	0,273	1,741	0	0	0	0
	8	1,301	5,941	0	0	0	0
	32	N.S.	<0,001	0	0	0	0
L-OHP	0	0,03	0,223	0	0	0	0
	1	0,171	0,791	0	0	0	0
	2	0,542	0,202	0	0	0	0
	4	N.S.	<0,001	0	0	0	0
	8	0,013	0,13	0	0	0	0
	32	0,122	0,422	0	0	0	0

m-moyenne ; s-écart type ; n-1 de Student ; N.S.-non significatif au seuil de p= 0,05
[] en ppm

ANALYSE DE METAPHASES IN VITRO SUR LYMPHOCYTES HUMAINS
RECHERCHE D'ACTIVITE GENOTOXIQUE EN ABSENCE D'ACTIVATION METABOLIQUE

PRODUITS	DOSES µM	GAPS PAR CELLULE	BREAKS PAR CELLULE	NOMBRE DE CELLULES ANORMALES/ NOMBRE DE CELLULES OBSERVEES	TOTAL DES ANOMALIES NOMBREES	NOMBRE TOTAL DE CELLULES PORTANT DES ANOMALIES DE STRUCTURE	
						EXCLUANT LES CELLULES A GAPS SEULS	INCLUANT LES CELLULES A GAPS SEULS
TENUON	0	0,045	0,045	0	0	0	0
	1	0,206	0,231	0	0	0	0
	2	0,01	2,07	0	0	0	0
MITOMYCINE C [1]	0,25	0,7	2,466	0	0	0	0
	1	1,07	0,23	0	0	0	0
	2	<0,05	<0,001	0	0	0	0
L-OHP	0	0,03	0,24	0	0	0	0
	1	0,101	1,150	0	0	0	0
	2	1,27	0,629	0	0	0	0
	4	<0,05	<0,001	0	0	0	0
	8	0,03	0,33	0	0	0	0
	32	0,171	0,731	0	0	0	0

m-moyenne ; s-écart type ; n-1 de Student ; N.S.-non significatif au seuil de p= 0,05
[] en ppm

4. Thybaud et al., Oxaliplatin (RP 54,780) in vitro mutagenicity test. Ames test. Rhone Poulenc Int. Rep. 176-E, 1988.

Salmonella typhimurium strains TA1535, TA1537, TA 1538, TA9S and TA100 were tested with up to 50 ug/plate of oxaliplatin (cytotoxic limit) with/without S9 activation with appropriate positive controls. No statistically significant increase in revertants were noted in any line tested.

STRAINS	50 µM	Controls		Test compound concentrations					
		Negative	Positive	0.12	0.25	0.5	1	2	5
TA1535	-	20	226	17	21	20	13	10	
TA100	-	146	613	136	136	146	76	64	
TA1537	-	7	226	5	7	11	9	7	
TA1538	-	9	226	14	13	8	6	2	
TA98	-	34	266	19	19	15	20	14	

Summary and Evaluation of Genotoxicity:

While oxaliplatin was negative in the Ames test, all other genotoxicity tests, mammalian TK locus mutations, mouse micronucleus, metaphase analysis were positive. Relative mutagenicity/clastogenicity was within an order of magnitude of cisplatin.

Overall Summary and Evaluation

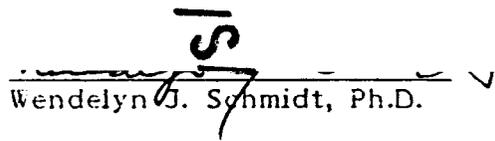
Oxaliplatin is a diaminocyclohexane derivative of cisplatin with decreased cross-resistance with cisplatin, increased solubility, and a spectrum of activity similar to cisplatin at equivalent doses both in vitro and in vivo. Thus, with similar antitumor activity, the toxicities can be legitimately compared for similar doses, which is not necessarily the case for carboplatin. The success of the day 1, 5 and 9 treatment regimen may be linked to the extensive protein binding and persistence of platinum content in tissues: by the second and third administration of oxaliplatin, the majority of available protein binding sites are occupied, leading to a higher concentration of active, unbound platinum drug to diffuse into cells.

In comparing plasma AUC levels across species, i.v administration led to comparable dose-normalized levels in the mouse and human. Rat levels by the i.p. route were approximately double. In the human, i.v. and i.p. routes led to similar levels of platinum in the plasma. The caveat here is whether the free or total platinum concentration was measured, as the free platinum has a half-life of less than 10 minutes in rodents. Tissue distribution studies indicated a lower level of drug in the kidney and liver than noted with cisplatin or carboplatin. Levels of platinum in spleen, kidney and liver remained relatively constant for over 96 hours, while levels of platinum in the gi tract decreased. While elimination measurements were not performed in the rodent, the decrease in gi tract platinum suggests some excretion via the feces, while humans excreted approximately 40% of the dose of oxaliplatin in the urine within the first 24 hours.

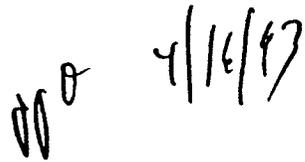
Toxicities of oxaliplatin in the rat and dog with multiple doses included relatively low toxicity to the hematopoietic system and the kidney. However, ataxias, testicular damage, and severe vomiting were observed. At high doses, deaths within 24 hours of drug administration were attributable to cardiac arrest, possibly secondary to hypokalemia. The major toxicities in the human were peripheral neuropathies, nausea and vomiting, and relatively low levels of marrow toxicity. While oxaliplatin was negative in the Ames test, mutagenicity and clastogenicity were demonstrated in the TK locus of mammalian cells, metaphase chromosome analysis of human lymphocytes, and mouse micronucleus test.

Recommendations

There are no new recommendations to the sponsor.


 Wendelyn J. Schmidt, Ph.D.

cc:
 IND ORIG.
 HFD-150
 /CSO
 /MO
 /JDeGeorge



Demographic Worksheet

Application Information (Enter all identifying information for the submission pertaining to this summary)

NDA Number: 21-492 Submission Type: N/A (pilot) Serial Number: N/A (pilot)

Populations Included In Application (Please provide information for each category listed below from the primary safety database excluding PK studies)

CATEGORY	NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG	
	Gender	Males	All Females	Females >50	Females >12	Females >65
Gender	Males	256	All Females	189	Females >50	141
Age:	0-≤1 Mo.	0	>1 Mo.-≤2Year	0	>2-≤12	0
	12-16	0	17-64	293	≥65	152
Race:	White	387	Black	30	Asian	10
	Other	18				

Gender-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on gender recommended in the label?

If the analysis was completed, who performed the analysis

Was gender-based analysis included in labeling?	
YES	NO
<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>

Yes

No

Sponsor

FDA

Age-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on age recommended in the label?

If the analysis was completed, who performed the analysis

Was age-based analysis included in labeling?	
YES	NO
<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>

Yes

No

Sponsor

FDA

Race-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on race recommended in the label?

If the analysis was completed, who performed the analysis

Was race-based analysis included in labeling?	
YES	NO
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>

Yes

No

Sponsor

FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

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

/s/

Mark Rothmann
8/7/02 10:18:47 AM

Amna Ibrahim
8/9/02 02:04:17 PM

STATISTICAL

Joint review with
Clinical

See Clinical Review
Section