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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 21-492

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-492

Drug:	Eloxatin
Generic Name:	Oxaliplatin for injection; cis-[(1*R*,2*R*)-1,2-cyclohexanediamine-N,N']][oxalato(2-)-*O*,*O*']
Formulation:	lyophilized powder containing 50 or 100 mg of oxaliplatin for reconstituion.
Indication:	Eloxatin in combination with 5-FU/LV is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial 5-FU/LV plus irinotecan
Applicant:	Sanofi-Synthelabo Inc.
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	05/17/02;
Primary/Pharmacometric Reviewer:	Brian Booth, Ph.D.
Team Leader:	N.A.M. Atiqur Rahman Ph.D.
Type of Submission:	Original NDA (category SE2 P)

I. Executive Summary

The applicant submitted the original NDA 21-492, ELOXATIN seeking marketing approval for the use of ELOXATIN in combination with 5-Fluoruracil and leucovorin (5-FU/LV) to treat patients with metastatic colorectal cancer that has recurred or progressed following initial 5-FU/LV plus irinotecan therapy.

A. Overall Recommendations

The clinical pharmacology and biopharmaceutics information submitted in the NDA is acceptable from the perspective of the Office of Clinical Pharmacology and Biopharmaceutics. The results of the renal study indicate that renal impairment progressively results in larger increases the plasma exposure of total platinum derived from Eloxatin, compared to patients with

normal renal function. Renal impairment may have a deleterious effect on safety. The applicant should incorporate the labeling changes indicated by FDA.

/S/

Reviewer: Brian Booth, Ph.D.

/S/

Team Leader: NAM Atiqur Rahman, Ph.D.

CC: NDA 21-492
HFD-150/Division File
HFD-150/WilsonC, IbrahimA, CohenM, Griebel D
HFD-860/MehtaM, MarroumP, RahmanNAM, BoothB

CDR/Biopharm

II. Table of Contents

III. Summary of the Clinical Pharmacology Findings

Eloxatin is an organoplatin compound that cross-links cellular macromolecules such as proteins and DNA to induce cell death via apoptosis. The pharmacokinetics of Eloxatin were originally reviewed in NDA 21-063. The current submission addressed several shortcomings identified in the first NDA. Using a validated assay, the applicant demonstrated that the pharmacokinetics of platinum from Eloxatin at 85 mg/m^2 are described by a three-compartment open mammallian model with a terminal elimination half-life of 391 hours. Eloxatin is rapidly hydrolyzed in vivo to yield a number of active and inactive platinum species. Cytchrome P-450 isozymes do not metabolize Eloxatin, and the platinum is excreted predominantly via the renal route (over 50% in 5 days). The pharmacokinetics of platinum from Eloxatin are not affected by 5-FU, nor are the pharmacokinetics of 5-FU affected by Eloxatin at a dosage of 85 mg/m^2. Eloxatin is extensively protein bound, but it did not mediate displacement interactions with erythromycin, salicylate, valproate, granisetron or paclitaxel.

The applicant conducted a study to assess the effect of renal impairment on the pharmacokinetics of Eloxatin in patients with a variety of cancers using a dose-escalation scheme and renal impairment criteria that differed from the FDA-promulgated recommendations. Re-analysis by FDA indicated that the $AUC_{0\text{-}48hr}$ of platinum in patients with mild, moderate and severe renal impairment increased 59, 138 and 191% respectively, compared to patients with normal renal function. Dose reductions based on this data have been suggested, but due to uncertainty regarding the effect of renal impairment on the different active platinum species of Eloxatin, a clinical decision will be necessary to decide on the need to dose reductions in patients with renal impairment.

IV. Question Based review

A. Background

Eloxatin is organoplatinum complex in which the platinum (Pt) atom is complexed with 1,2-diaminocyclohexane (DACH) and an oxalate leaving group.

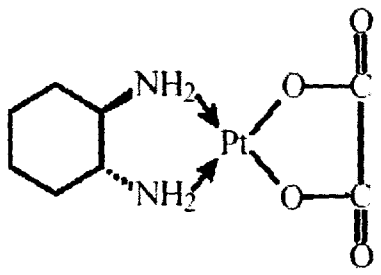


Figure 1. Eloxatin; oxaliplatin MW 397.3

The Clinical Pharmacology of Eloxatin was extensively reviewed in NDA 21-063. Eloxatin, like cisplatin, mediates its action by cross-linking cellular macromolecules. Upon administration, Eloxatin undergoes hydrolysis to yield a number of Pt –containing metabolites. The pharmacokinetics of Eloxatin are described by a three-compartment model with $t_{1/2}$'s of 0.43, 16.8 and 391 hours. The pharmacokinetics of Eloxatin appear to be linear between 40 and 130 mg/m^2. Eloxatin does not undergo cytochrome P-450 metabolism, nor does it inhibit any cytochrome P-450 isozymes. Therefore, no cytochrome P-450 based drug-drug interactions are anticipated. The extent of Eloxatin plasma protein binding is approximately 90 to 95 % in vivo, and Pt accumulates in erythrocytes with repeated administration of Eloxatin, although there is no apparent adverse reaction associated with accumulation. Eloxatin is eliminated primarily by renal excretion. Approximately 50 % of Pt is excreted in the urine after a single dose of Eloxatin. Age and gender had no apparent affect on the pharmacokinetics of Eloxatin.

In the original review of Eloxatin, several issues were raised by the Office of Clinical Pharmacology and Biopharmaceutics. These were addressed in the currnet submission as follows

- The original study indicated a small interaction between 130 mg/m^2 Eloxatin and 5-FU that raised 5-FU concentrations by 20-25%, based on a study that employed an unconventional 5-FU dosing regimen. The applicant has since deleted the 130 mg/m^2 Eloxatin dosing recommendation in the product labeling, and no additional study is apparently needed.

- The effect of renal impairment on the pharmacokinetics of Eloxatin needed clarification. The applicant included a renal impairment study in the current submission.

- The applicant employed an assay that provides the pharmacokinetics of total platinum. Although the applicant validated an updated version of the method, total platinum is measured. An assay with a different type of separation/detection would be necessary to assess the pharmacokinetics of the active platinum species. Currently, this approach may not be available.

- Eloxatin appears to undergo hydrolysis, a prolonged circulation in the patient and then renal excretion. In the original submission, the applicant did not completely rule out other metabolic routes. No additional data has been submitted.

- In the Eloxatin-5-FU interaction study, granisetron was used prophyllactically. This finding suggested that this anti-emetic may have contributed to the apparent drug-drug interaction observed, although there is no apparent cytochrome P-450 basis for this interaction. This was not studied further.

- A simulation was used in the original study to support dosing instructions for 85 mg/m^2 Eloxatin. The applicant submitted a pharmacokinetic study of 85 mg/m^2 in patients with gastrointestinal cancer to support dosing instructions in the labeling.

B. Does renal impairment affect the pharmacokinetics of Eloxatin?

Yes. The applicant conducted a pharmacokinetic study of Eloxatin in renally-impaired patients. Thirty-seven patients with a variety of cancers and with normal to severely impaired renal function were studied with Eloxatin doses ranging from 60 to 130 mg/m^2 (see Table 1).

Table 1. Renal Function and Eloxatin Dosing

Table 5.1-1 Treatment Plan		
Group	**Creatinine Clearance**	**Starting Dose of Oxaliplatin and Escalation Plan**
A (normal controls)	> 60 mL/min	130 mg/m^2
B (mild dysfunction)	40 to 59 mL/min	105 mg/m^2 130 mg/m^2
C (moderate dysfunction)	20 to 39 mL/min	80 mg/m^2 105 mg/m^2 130 mg/m^2
D (severe dysfunction)	< 20 mL/min	60 mg/m^2 80 mg/m^2 105 mg/m^2 130 mg/m^2

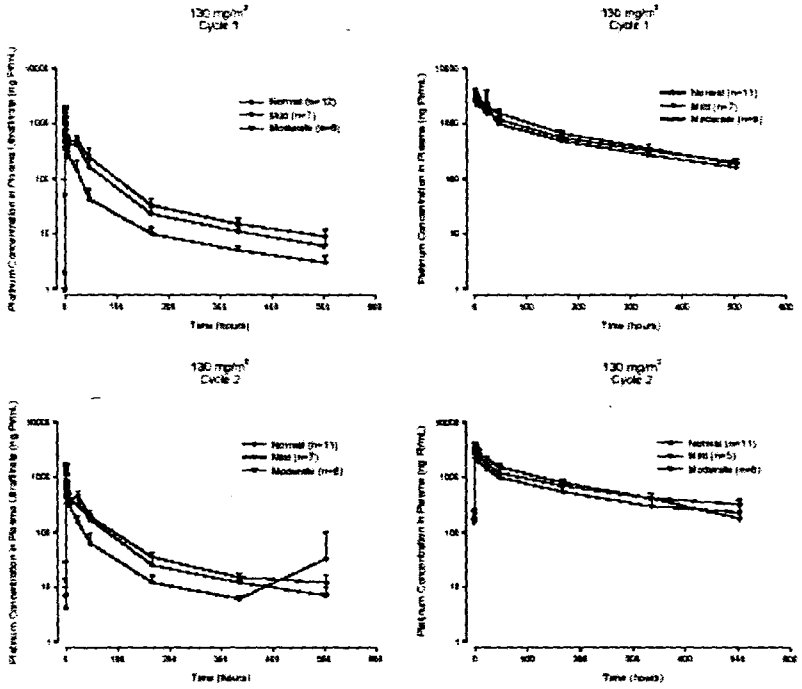


Figure (7.2) 1 - Comparative Mean ± SD Plasma Ultrafiltrate (left hand panels) and Plasma (right hand panels) Platinum Concentrations in Patients with Normal, Mild and Moderate Renal Function Receiving 130 mg/m^2 Oxaliplatin on cycle 1 (upper panels) or cycle 2 (lower panels)

Figure 2. Applicant's Comparison ultrafiltrate and plasma concentrations of platinum in patients with normal, mild, and moderate renal impairment.

Table 2. Applicant's summary of Platinum pharmacokinetics in plasma

Table (7.4) 2 - Summary of Mean Non-Compartmental Pharmacokinetic Parameters of Platinum in Plasma

Cycle	Renal Status	Dose (mg/m^2)	No. of Subjects	C_{max} (µg Pt /mL)	AUC_{0-48} (µg Pt .h/mL)	AUC (µg Pt .h/mL)	Vss (L)	Cl (L/h)
1	Normal	130	10	3.94 (1.53)	89.5 (45.3)	313 (79.2)	73.9 (21.9)	0.413 (0.154)
	Mild	105	3	3.32 (1.23)	57.3 (23.9)	278 (83.8)	78.6 (46.2)	0.338 (0.0417)
		130	6	3.65 (0.367)	83.3 (12.4)	382 (26.0)	67.7 (23.5)	0.294 (0.0214)
	Moderate	80	2	2.31 (0.629)	65.2 (0.358)	267 (23.4)	51.4 (22.6)	0.241 (0.0138)
		105	2	3.68 (1.07)	80.5 (19.7)	233 (58.5)	53.9 (15.0)	0.458 (0.136)
		130	5	4.10 (0.412)	104 (10.5)	416 (58.4)	68.4 (17.9)	0.318 (0.0559)
	Severe	60	1	1.76 (NA)	42.6 (NA)	198 (NA)	76.4 (NA)	0.265 (NA)
2	Normal	130	8	3.35 (0.488)	74.6 (11.2)	332 (83.1)	77.8 (19.9)	0.397 (0.141)
	Mild	105	2	2.94 (0.389)	68.6 (6.17)	350 (41.6)	74.2 (16.2)	0.249 (0.0358)
		130	5	3.34 (0.672)	85.9 (21.2)	395 (81.7)	63.2 (25.8)	0.296 (0.0693)
	Moderate	80	3	2.46 (0.336)	65.6 (12.2)	269 (70.5)	47.7 (9.56)	0.240 (0.0588)
		105	1	3.08 (NA)	70.4 (NA)	241 (NA)	71.5 (NA)	0.413 (NA)
		130	5	3.93 (0.109)	106 (11.6)	439 (51.2)	64.6 (10.2)	0.280 (0.0465)
	Severe	60	1	1.70 (NA)	48.6 (NA)	214 (NA)	48.9 (NA)	0.245 (NA)

NA= not applicable

Applicant's Conclusions:

- 130 mg/m2 Eloxatin was well tolerated.
- Prolonged treatment with Eloxatin may cause renal deterioration, as suggested by the elevated creatinine clearance observed in two patients after the fifth cycle of therapy.
- Renal function had no effect on C_{max}.
- Ultrafiltrate AUC increased significantly with renal impairment, but there was no clinically significant increase in toxicity.
- No dose reductions appear warranted.

FDA Analysis

There are several issues regarding the applicant's analysis of the data that raise questions about the results and conclusions

- Stratification of renal impairment severity. The applicant used a different stratification for renal impairment than the one promulgated by the FDA (refer to the Guidance for Industry entitled "Pharmacokinetic studies in patients with impaired renal function").
- A mini-dose escalation approach was used instead of the approaches recommended by FDA. The use of multiple doses of Eloxatin in these studies make interpretation more difficult. Furthermore, the goal of these studies was to achieve dosages of 130 mg/m^2, which is higher than the labeled dose of the drug.
- The applicant used the Cockcroft-Gault formula to calculate creatinine CL (CLcr) in the patients, but the expression for males was used in patients of either sex [(CLcr = ((140-age)*weight)/(72*serum creatinine)]. Of the 34 patients in the database, 11 were female patients.

In the FDA re-analysis, the following steps were implemented

- Creatinine clearance was re-calculated for female patients according to the Cockcroft-Gault equation (CLcr= (140-age)*weight)/(85*serum creatinine).
- Patients were re-stratified according to the FDA Guidance.
- C_{max}, AUC_{0-48} and AUC were normalized to dose.

Results

Table 3. Plasma Pharmacokinetics of Eloxatin During Cycle 1

Parameter	Normal n = 6	Mild Impair. N = 6	Moderate impair. N= 11	Severe impair. N=5
C_{max}/dose	0.0138 ± 0.002	0.0145 ± 0.0016	0.0172 ± 0.048	0.0177 ± 0.0023
% of normal	na	+5.1%	+24.6%	+28.3%
AUC_{0-48}/dose	0.304 ± 0.05	0.272 ± 0.121	0.365 ± 0.079	0.466 ± 0.044
% of normal	na	-10.5%	+20%	+53%
AUC_{∞}/dose	1.23 ± 0.33	1.44 ± 0.36	1.44 ± 0.25	1.94 ± 0.19
% of normal	na	+17%	+17%	+57.7%

Table 4. Plasma Pharmacokinetics of Eloxatin During Cycle 2

Parameter	Normal n = 6	Mild Impair. N = 6	Moderate impair. N= 11	Severe impair. N=5
C_{max}/dose	0.0134 ± 0.0024	0.0136 ± 0.0011	0.0158 ± 0.025	0.0177 ± 0.0027
% of normal	na	+1.5%	+18%	+32%
AUC_{0-48}/dose	0.296 ± 0.069	0.327 ± 0.029	0.394 ± 0.065	0.49 ± 0.069
% of normal	na	+10%	+33%	+66%
AUC_{∞}/dose	1.36 ± 0.49	1.6 ± 0.31	1.72 ± 0.4	2.05 ± 0.36
% of normal	na	+18%	+27%	+51%

Table 5. Plasma Ultrafiltrate Pharmacokinetics of Eloxatin During Cycle 1

Parameter	Normal n = 8	Mild Impair. N = 6	Moderate impair. N= 11	Severe impair. N=4
C_{max}/dose	0.0052 ± 0.0011	0.0063 ± 0.002	0.0522 ± 0.0019	0.00633 ± 0.0017
% of normal	na	+21%	0%	+22%
AUC_{0-48}/dose	0.0343 ± 0.010	0.054 ± 0.013	0.081 ± 0.022	0.099 ± 0.012
% of normal	na	+59%	+138%	+191%
AUC_{∞}/dose	0.0623 ± 0.024	0.103 ± 0.025	0.187 ± 0.072	0.25 ± 0.03
% of normal	na	+65%	+200%	+300%

Table 6. Plasma Ultrafiltrate Pharmacokinetics of Eloxatin During Cycle 2

Parameter	Normal n = 6	Mild Impair. N = 5	Moderate impair. N= 9	Severe impair. N=5
C_{max}/dose	0.005 ± 0.0015	0.0065 ± 0.002	0.0059 ± 0.0012	0.006 ± 0.0015
% of normal	na	+30%	18%	+20%
AUC_{0-48}/dose	0.038 ± 0.008	0.05 ± 0.011	0.070 ± 0.019	0.105 ± 0.03
% of normal	na	+31.5%	+84%	+176%
AUC_{∞}/dose	0.081 ± 0.035	0.145 ± 0.045	0.167 ± 0.042	0.202 ± 0.117
% of normal	na	+79%	+106%	+149%

FDA Conclusion

These data indicate a very large pharmacokinetic effect of renal impairment on Eloxatin. The applicant reported that no clinically significant adverse events were reported although these results were not re-stratified. Unfortunately, the study is likely too small to detect significant changes in toxicity. In the first cycle of therapy, data on platinum in plasma ultrafiltrate was derived from only six patients with mild renal impairment, 11 with moderate impairment, and only four patients with severe renal impairment. Despite these small numbers, the variability in the AUC_{0-48} measurements was 24, 27 and 12 %CV, respectively. This low variability indicates that AUC_{0-48} is a reliable gauge of the effect of renal impairment on platinum exposure in the patient. Clearly, renal impairment leads to increased platinum exposures beyond the level normally observed in patients with healthy renal function. In these studies, two patients experienced increased serum creatinine concentrations after five cycles of therapy that prompted their withdrawal from Eloxatin. However, the cause of these adverse events could not be specifically ascribed to Eloxatin because of pre-existing renal conditions in each patient.

Eloxatin will be administered in conjunction with 5-FU and leucovorin, and the safety studies in this submission indicate that the toxicities experienced with the combination were additive or synergistic with each other. Because the renal impairment study was conducted with Eloxatin alone, it is possible that the combination of Eloxatin and 5-FU in renal impairment may result in more severe adverse events than the combination alone, especially if the toxocoties are dsoe-related. Further, the applicant reported that 130 mg/m^2 Eloxatin may have increased 5-FU plasma concentrations by 20 to 25% in a drug-drug interaction study. This situation may be exacerbated in patients with renal impairment by the higher total platinum exposures experienced by this group. In Europe and Australia, Eloxatin is approved for colorectal cancer. However, use of Eloxatin is contraindicated in patients with severe renal impairment on both continents. In Europe, caution is advised in treating patients with moderate renal impairment, and unspecified dose adjustment is advised if toxicities are observed in patients.

The observed changes in the $AUC_{0\text{-}48h}$ were for total platinum, and these data could not be interpreted easily. Ideally, the applicant would have characterized the pharmacokinetics of the active Pt species, so that the effect of renal impairment could be readily determined. In vitro studies in this submission (MIV250) indicate that Eloxatin is the major component in plasma ultrafiltrate when the drug is administered (70%; total recovered 87%). After four hours of incubation, the majority of the species are Eloxatin (24%), diaquo DACH platin (13%, an active species) and a mixture of monoaquo and methionine DACH platin (12%, one active, one inactive species, respectively). Therefore, the effects of renal impairment on total platinum may not reflect changes in each of the active Pt species, but it seems likely that renal impairment would have some impact each individual species of platinum. In order to maintain the $AUC_{0\text{-}48h}$ of total ultrafiltrate platinum of patients with renal impairment with a comparable $AUC_{0\text{-}48h}$ in patients with normal renal function, the doses of Eloxatin could be reduced to

- 53.5 mg/m2 in patients with mild renal impairment,
- 35.7 mg/m2 in patients with moderate impairment,
- 29.2 mg/m2 in patients with severe renal impairment

However, given the possibility that the total platinum may not reflect changes for each species of platinum, a clinical decision concerning the safety data and the need for dose adjustments in patients with renal impairment should be made.

C. Are the pharmacokinetics of Eloxatin at the proposed dose adequately described?

Only partly. The shortcoming in these studies was that the active platinum species of Eloxatin were not characterized, and total platinum reflects the pharmacokinetics of active and inactive species of platinum. The applicant conducted a phase 1 pharmacokinetic study of Eloxatin at 85 mg/m^2 in combination with 5-Fluorouracil (5-FU) in nine patients with gastrointestinal carcinoma and normal renal function. Eloxatin was administered as a 2-hour infusion once every two weeks (q2w), and 5-FU was administered as a continuous infusion of 300 mg/m^2/day for 12 weeks of a 12-week cycle.

Data from six patients was considered evaluable. Two patients completed fewer than three cycles of therapy and one patient was dosed with 100 mg/m^2 of Eloxatin. The data from these patients was omitted from the analysis.

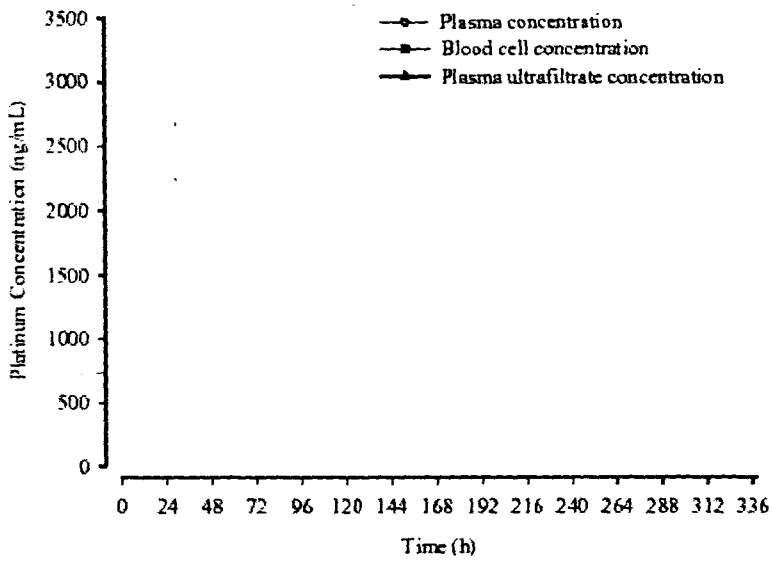


Figure 3. Concentration vs. time curves for Platinum in plasma, plasma ultrafiltrate and blood cells during the first cycle of Eloxatin.

Table 4. Applicant's Summary of Lpatinum Pharmacokinetics

Table (8.2.1) 1 - Summary of Platinum Pharmacokinetic Parameter Estimates in Plasma Ultrafiltrate, Plasma, Blood Cells and Whole Blood Following Multiple Doses of Oxaliplatin at 85 mg/m^2 q2w

Matrix	C_{md} (µg/mL)	C_{max} (µg/mL)	AUC_{0-48} (µg/mL.h)	AUC (µg/mL.h)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	V_{ss} (L)	CL (L/h)	CL_{0-48} (L/h)
Ultrafiltrate										
Mean	0.814	0.814	4.19	4.68	0.434	16.8	391	440	17.4	6.86
SD	0.193	0.193	0.647	1.40	0.347	5.74	406	199	6.35	2.45
Plasma										
Mean	2.03	2.12	47.2	123	0.471	19.3	281	NA	0.687	NA
SD	0.344	0.319	5.10	49.0	0.350	4.96	99.6	NA	0.368	NA
Blood Cells*										
Mean	2.64	2.71	105	624	NA	NA	NA	NA	NA	NA
SD	0.591	0.482	17.8	159	NA	NA	NA	NA	NA	NA
Blood										
Mean	2.29	2.31	72.5	257	0.806	21.3	771	NA	0.276	NA
SD	0.156	0.148	6.91	31.3	0.583	5.34	183	NA	0.0755	NA

NA: Not applicable

Mean AUC_{0-48}, C_{md}, and C_{max} values were determined on Cycle 3.

Mean AUC, V_{ss}, CL, and CL_{0-48} values were determined on Cycle 1.

C_{md}, C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis.

$t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined by compartmental analysis (Cycles 1-3 combined).

* Platinum levels in blood cells derived from values in whole blood using a nominal hematocrit of 0.44.

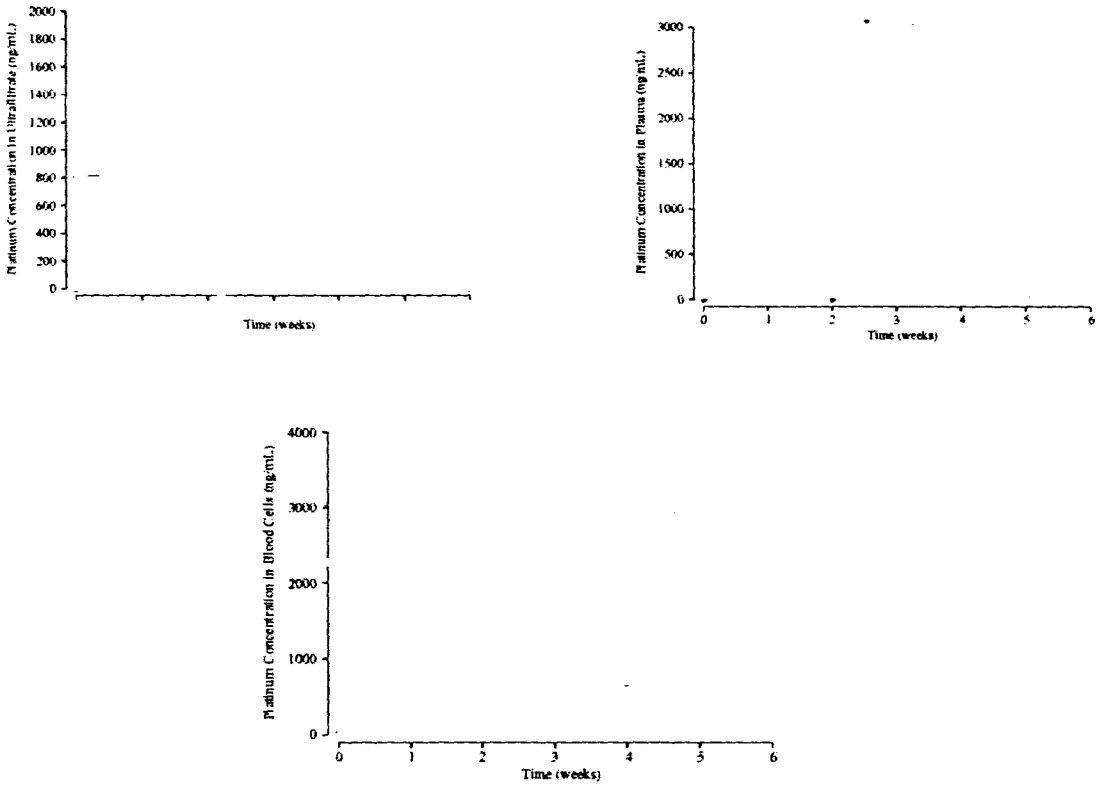


Figure 4. Applicant's concentration vs time curves for platinum in ultrafiltrate, plasma and blood cells

Table 7. Applicant's comparison of whole blood AUC_{0-48} from cycle 1 to cycle 3

Table (8.2.2.4.2) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for AUC_{0-48} in Whole Blood

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	44.7	72.2	79.8
23	39.7	56.6	71.6
24	36.5	44.0	63.8
26	42.1	65.0	76.7
27	39.8	57.1	78.3
29	45.5	59.3	64.8
Mean AUC_{0-48} (µg.h/mL)	41.4	59.0	72.5
SD	3.41	9.44	6.91
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	1.75 (1.58, 1.93)		
Cycle 1 vs. Cycle 3	0.572 (0.52, 0.63)		
Cycle 2 vs. Cycle 3	0.810 (0.73, 0.89)		

REF: Appendix 6.2.3

Table 8. Applicant's summary of renal Clearance of Platinum

Table (8.2.3) 1 - Summary of Platinum Renal Clearance and Percentage of the Dose Excreted in the 0-48h interval

Patient	CL_{0-48} (L/h)	% Dose Excreted in 48 Hours	% Dose Excreted in 24 Hours
21	11.7	48.4	44.8
23	6.22	28.2	24.0
24	5.41	39.9	35.7
26	6.06	39.4	34.4
27	6.72	24.4	17.6
29	5.04	27.2	17.8
Mean	**6.86**	**34.6**	**29.1**
SD	**2.45**	**9.41**	**11.0**

REF: Appendices 6.2.2.5 and 6.2.3

Total platinum does not significantly accumulate in the ultrafiltrate or the plasma with repeated Eloxatin dosing. The applicant's analysis suggested significant accumulation of total platinum in the blood cells. However, the extent of accumulation determined by the applicant is unreliable because these data were calculated using a fixed hematocrit of 0.44 (Blood cell Pt = whole blood Pt –[plasma Pt(1-hematocrit)]/hematocrit). This approach is likely to produce erroneous results because females typically have a lower hematocrit than males, and several of the patients suffered anemia. Therefore, the whole blood measurements of total platinum are likely more reflective of accumulation. These data indicate that there is a 1.75 fold accumulation of total platinum in whole blood by the third cycle of therapy. In vitro studies have demonstrated that erythrocytes accumulate platinum, which may potentially become a problem with prolonged use of Eloxatin, although no adverse events were reported in this study.

The urinary excretion of total platinum was approximately 30 % within 24 hours, which is consistent with the extent of excretion previously reported for patients dosed with 130 mg/m^2 Eloxatin in study PKM 2983 part 1 (approximately 37% in 24 hrs and 54% in 5 days).

The 5-FU dosing regimen differs from regimen recommended in the labeling for Eloxatin. From the pharmacokinetic perspective, this likely not significant because it was concluded in the previous review of Eloxatin that 5-FU did not affect the pharmacokinetics of total platinum.

The effect of Eloxatin on the pharmacokinetics of 5-FU was not addressed in the new study. The previous review of Eloxatin evaluated two drug-drug interaction studies conducted by the sponsor. The first study indicated no effect of 85 mg/m^2 Eloxatin on 5-FU pharmacokinetics, whereas the second study of 130 mg/m^2 suggested that 5-FU plasma concentrations may be elevated by 20-25%. The labeling of Eloxatin has been amended since the first submission of Eloxatin to recommend only 85 mg/m^2 of Eloxatin in combination with the de Gramont regimen of 5-FU/leucovorin. Therefore, the possible interaction between Eloxatin and 5-FU at the higher dosage is not clinically relevant.

D. Were the Analytical Methods acceptable for the determination of the plasma concentrations of Eloxatin?

Only partly. The assay used in the clinical pharmacology studies quantified only total platinum, but not the active platinum species of Eloxatin. The applicant used Inductively Coupled Plasma Mass Spectrometry (ICPMS) to assay platinum derived from Eloxatin. The applicant re-validated this assay for use in plasma, plasma ultrafiltrate and urine because a new method of _____ was developed. These new assays were used in the renal impairment study POP7488, and the old assays were cross-validated with the new assays to ensure comparability of the data among studies. Overall the methods for total platinum were well-validated. The most important drawback of these assays is that they are specific for platinum, but not for Eloxatin or a specific metabolite of Eloxatin. Therefore, only total platinum pharmacokinetics (active plus inactive species of platinum) can be determined. A new methodological approach would be necessary to overcome this shortcoming. The assay was validated from 1 to 1000 ng/ml in plasma ultrafiltrate, 100 to 10000 ng/ml in plasma and 100 to 25000 ng/ml in urine.

V. FDA Labeling

1. Applicant's Labeling

FDA Labeling
CLINICAL PHARMACOLOGY, Human pharmacokinetics, line 52

Dose	C_{max} (µg/mL)	AUC_{0-48} (µg/mL.h)	AUC_{0-inf} (µg/mL.h)	V_{ss} (L)	Cl (L/h)
85 mg/m^2					
Mean	0.814	4.19	4.68	440	17.4
SD (n=6)	0.193	0.647	1.40	199	6.35

Reason: We have included the number of patients that the data was derived from for completeness.

2. Applicant's Labeling

FDA Labeling
CLINICAL PHARMACOLOGY, distribution.
At the end of a 2-hour infusion of ELOXATIN, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine.

In patients, plasma protein binding of platinum is irreversible and is greater than 90%.

The main binding proteins are albumin and gamma-globulins. Platinum also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes. Platinum bound to erythrocytes is not considered to be of clinical significance. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks

Reason: The applicant's description of protein binding was confusing and incomplete without the complete timecourse description. The absolute extent of platinum binding is of minimal clinical significance in this instance and therefore a simple statement would be best.

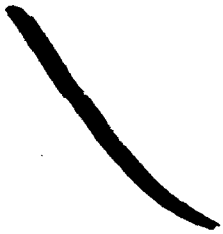
3. Applicant's Labeling

FDA Labeling
CLINICAL PHARMACOLOGY, Pharmacokinetics in special populations.

The $AUC_{0\text{-}48hr}$ of platinum in the plasma ultrafiltrate increased as renal function decreased. The $AUC_{0\text{-}48hr}$ of platinum in patients with mild (creatinine clearance, CL_{cr} 50 to 80 ml/min), moderate (CL_{cr} 30 to <50 ml/min) and severe renal (CL_{cr} <30 ml/min) impairment increased 60, 140 and 190% respectively, compared to patients with normal renal function (>80 ml/min).

Reason: The passage was completely changed because FDA did not agree with the applicant's choice of renal impairment stratification or the use of male expression of Cockcroft-Gault creatinine clearance calculation for all patients. FDA re-calculated creatinine clearance for female patients, and re-stratified the renal impairment according to the FDA guidance, and these data are now presented in the current section of the labeling.

4. Applicant's Labeling



FDA Labeling
CLINICAL PHARMACOLOGY, Drug-Drug interactions line 98

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

VII. Study Synopses

DOH0234 Analytical Validation Study
[redacted] January 31, 2002

Matrix: Plasma ultrafiltrate
Matrix digestion: [redacted]
Anticoagulant: Na hep
Method: Inductively coupled plasma mass spectrometry ICP-MS [redacted]

[redacted]

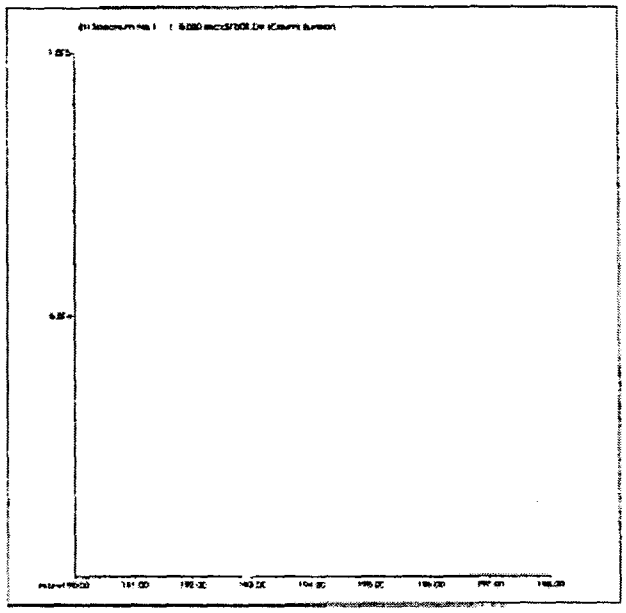
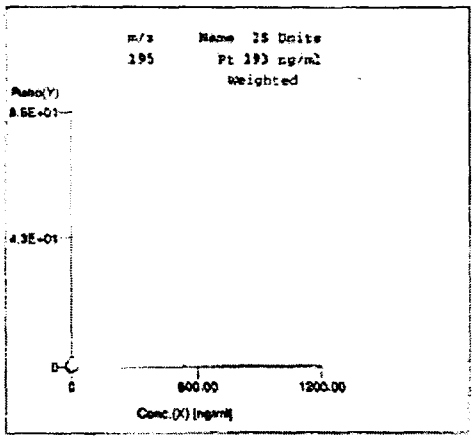


Figure (6.2) 1 - Representative ICP-MS scan of ^{194}Pt, ^{195}Pt and ^{193}Ir in human plasma ultrafiltrate containing [redacted] ng/mL of platinum (LLOQ) and [redacted] ng/mL of iridium internal standard

Range 1 to 1000 ng/ml



Lv.	Conc.	Ratio	RSD %
1	1.00	1.14E-1 P	5.79E-1
2	1.00	1.07E-1 P	4.66E-1
3	1.00	1.13E-1 P	1.13
4	2.50	2.40E-1 P	8.20E-1
5	10.00	8.77E-1 P	2.38E-2
6	50.00	4.29E+0 P	4.45E-1
7	100.00	8.54E+0 P	3.78E-1
8	500.00	4.24E+1 P	1.59E-1
9	1000.00	8.52E+1 A	3.78E-1
10	1000.00	8.41E+1 A	1.05
11	1000.00	8.41E+1 A	8.62E-1
*12	---	---	---
*13	***	***	---
*14	---	---	---
*15	---	---	---
*16	---	---	---
*17	---	---	---
*18	---	---	---
*19	---	---	---
*20	---	---	---

CurveFit : Y=aX+b

Y = 8.514E-2*X +2.549E-2
X = 1.175E+1*Y -2.994E-1

MinConc: 0.00

Figure (6.2) 2 - Representative calibration curve for the quantification of platinum in human plasma ultrafiltrate

LOQ ng/ml
Blanks: pools from 6 different lots of plasma.

Accuracy and precision

Nominal amount (ng/ml.)	Mean calculated amount (ng/ml.)	Percent Accuracy (95% CI)	Within-run Percent Precision (95% CI)	Between-run Percent Precision (95% CI)	Total Percent Precision (95% CI)
1	0.880	-11.9 (-16.6, -7.19)	1.25 (0.90, 2.07)	5.01 (3.08, 12.4)	5.17 (3.32, 12.5)
2.5	2.39	-4.41 (-7.49, -1.33)	2.69 (1.91, 4.57)	2.62 (0.00, 7.34)	3.76 (2.80, 7.88)
100	103	2.69 (0.36, 5.03)	1.50 (1.08, 2.48)	1.98 (0.91, 5.23)	2.49 (1.80, 5.46)
1000	980	-1.96 (-3.52, -0.41)	1.21 (0.87, 2.00)	1.34 (0.43, 3.63)	1.80 (1.34, 3.85)

Dilution: up to 10000 ng/ml when diluted.

Nominal Concentration (ng/mL)	1000	1000	10000
Dilution	1:2 (500 ng/mL)	1:4 (250 ng/mL)	1:10 (1000 ng/mL)
Calculated concentration (ng/mL)			
Mean	524	269	1030.
%CV	2.91	1.01	0.397
M%D	4.83	7.53	2.83

Stability:
Storage: at least –
Freeze thaws: from previous assay, 3 cycles were acceptable. Deemed acceptable.
Frozen: at - from previous assay. Deemed acceptable
Benchtop: current study up to 24 and — hrs compared to frozen calibration curve.

Stability Assessment		Concentration (ng/mL)			
		2.5[a]	1000[a]	2.5[b]	1000[b]
24 h stability	Mean	2.54	1070	2.50	1060
	%CV	5.51	5.56	5.49	5.52
	M%D	1.60	6.63	-0.133	5.88
48 h stability	Mean	2.58	1050	2.58	1050
	%CV	1.72	3.01	1.72	3.01
	M%D	3.28	4.50	3.28	4.50
168 h stability	Mean	2.50	1030	2.34	986
	%CV	2.38	1.14	2.44	0.959
	M%D	0.00	2.83	-6.40	-1.40

[a] analysed against a freshly processed calibration curve
[b] analysed against a calibration curve processed at the same time as the samples

- carry-over

Carry-over determination	1000 ng/mL	1 ng/mL	1 ng/mL
Mean	988	1.03	1.04
%CV	4.03	7.18	7.19
M%D	-1.18	3.25	4.40

Crossvalidation

1. Oxaliplatin to commercial Pt.

Nominal Concentration (ng/mL)	Platinum Source	Mean Concentration (ng/mL)	Estimated Ratio	90% CI for Ratio
2.5	Platinum Standard	2.45	NC	NC
	Oxaliplatin	2.43	0.993	0.978, 1.01
1000	Platinum Standard	994	NC	NC
	Oxaliplatin	995	1.000	0.995, 1.01

NC; Parameter not calculated

2. Old ICP-MS assay to new ICP-MS assay

Stability Assessment		Concentration (ng/mL)	
	Nominal	3.01	201
——— ICP-MS assay	Mean	3.07	204
	%CV	7.60	0.693
	M%D	1.83	1.49
— ICP-MS assay	Mean	2.97	179
	%CV	0.859	0.594
	M%D	-1.41	-11.1

Conclusions:

1. Validated assay from 1 to 1000 ng/ml.
2. Cross-validated with commercial Pt, therefore, not specific for Oxaliplatin
3. Cross-validated with the old ——— ICP-MS assay.

Problems:

1. Still determining total PT and not drug alone (cannot distinguish between parent metabolites or Pt alone). This may not be a resolvable issue.
2. Spiked ultrafiltrate instead of spiking plasma and obtaining ultrafiltrate. May lead to underestimate of actual concentrations if there is a loss due to a recovery problem

Otherwise, the method is well validated.

Study DOH0233 Validation of ICP-MS for Pt in Human Plasma. Volume 23

January 2002.

Matrix: Plasma
Matrix digestion: ———
Anticoagulant: Na hep-no effect on concentration
Method: Inductively coupled plasma mass spectrometry ICP-MS

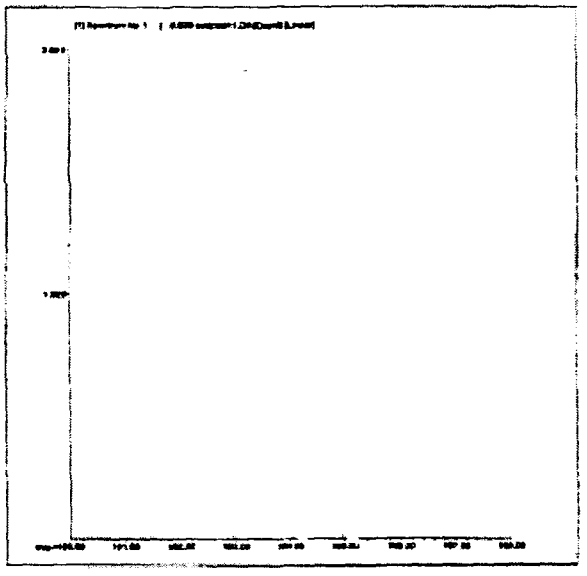
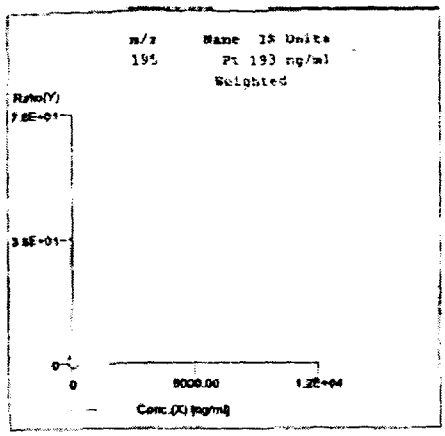


Figure (6.2) 1 – Representative ICP-MS scan of ^{194}Pt, ^{195}Pt and ^{193}Ir in human plasma containing ▬ ng/mL of platinum (LLOQ) and ▬ ng/mL of iridium internal standard.

Range 100 to 10000 ng/ml (100, 250, 500, 1000, 2500, 5000, 10000 ng/ml)



Lv.	Conc.	Ratio		RSD %
1	100.00	8.32E-1	P	3.24E-1
2	100.00	7.85E-1	P	3.33E-1
3	100.00	8.24E-1	P	9.59E-1
4	250.00	1.95E+0	P	7.27E-1
5	500.00	3.88E+0	P	3.78E-1
6	1000.00	7.57E+0	P	3.27E-1
7	2500.00	1.94E+1	P	1.40E-1
8	5000.00	3.90E+1	A	2.98E-1
9	1.00E+4	7.33E+1	A	7.17E-1
10	1.00E+4	7.41E+1	A	7.41E-1
11	1.00E+4	7.16E+1	A	9.07E-1
*12	---	---		---
*13	---	---		---
*14	---	---		---
*15	---	---		---
*16	---	---		---
*17	---	---		---
*18	---	---		---
*19	---	---		---
*20	---	---		---

CurveFit : Y=aX+b

Y = 7.701E-3*X +3.819E-2
X = 1.298E+2*Y -4.959E+0

MinConc: 0.00

Figure (6.2) 2 – Representative calibration curve for the quantification of platinum in human plasma

LOQ — ng/ml
Blanks: pools from 6 different lots of plasma.

Accuracy and precision

Nominal amount (ng/mL)	Mean calculated amount (ng/mL)	Percent Accuracy (95% CI)	Within-run Percent Precision (95% CI)	Between-run Percent Precision (95% CI)	Total Percent Precision (95% CI)
100	95.3	-4.74 (-7.12, -2.35)	2.20 (1.55, 3.73)	2.00 (0.00, 5.60)	2.97 (2.21, 6.07)
250	238	-4.87 (-7.18, -2.55)	1.51 (1.08, 2.49)	2.15 (1.06, 5.62)	2.63 (1.88, 5.83)
1000	970	-2.99 (-6.10, 0.13)	3.49 (2.50, 5.76)	2.30 (0.00, 7.21)	4.18 (3.24, 8.15)
10000	9480	-5.19 (-8.41, -1.97)	2.03 (1.45, 3.35)	3.02 (1.54, 7.85)	3.64 (2.99, 8.12)

Dilution: up to 10000 ng/ml when diluted.

Nominal Concentration (ng/mL)	10000	40000
Dilution	1:2 (5000 ng/mL)	1:4 (10000 ng/mL)
Calculated concentration (ng/mL)		
Mean	5010	11000
%CV	4.88	14.9
M%D	0.200	10.0

Bold underlined values are outside acceptance criteria of ± 15% of nominal.

Stability:
Storage: .
Freeze thaws: from previous assay, 3 cycles were acceptable. Deemed acceptable.
Frozen: at – from previous assay. Deemed acceptable
Benchtop: current study up to 24 and hrs compared to frozen calibration curve.

Stability assessment		Concentration (ng/mL)			
		250[a]	10000[a]	250[b]	10000[b]
24 h stability	Mean	240	10100	244	10200
	%CV	9.66	0.932	9.75	0.620
	M%D	-4.13	0.717	-2.40	2.00
48 h stability	Mean	250	9950	243	9620
	%CV	1.38	3.16	1.42	3.01
	M%D	0.133	-0.467	-2.67	-3.85
168 h stability	Mean	250	9770	242	9740
	%CV	1.56	3.86	1.56	3.94
	M%D	-0.2	-2.27	-3.33	-2.62

[a]Analysed against a freshly processed calibration curve.
[b]Analysed against a calibration curve processed at the same time as the samples

carry-over

Carry-over determination	10000 ng/mL	100 ng/mL	100 ng/mL
Mean	10000	107	99.2
%CV	0.520	11.3	1.91
M%D	0.050	7.18	-0.833

CrossValidation

1. Oxaliplatin and commercial Pt

Nominal Concentration (ng/mL)	Platinum Source	Mean Concentration (ng/mL)	Estimated Ratio	90% CI for Ratio
250	Platinum Standard	247	NC	NC
	Oxaliplatin	249	1.009	0.999, 1.019
10000	Platinum Standard	10040	NC	NC
	Oxaliplatin	10045	1.000	0.994, 1.007

2 old ICP-MS assay vs. new ICP-MS

Stability Assessment		Concentration (ng/mL)	
	Nominal	300	7500
1 ICP-MS assay	Mean	310	7640
	%CV	9.25	3.34
	M%D	3.39	1.71
ICP-MS assay	Mean	294	7590
	%CV	1.34	1.35
	M%D	-2.00	1.18

Problem:
1 Cannot distinguish between parent, metabolites and Pt alone.

DOH0211 Validation of ICP-MS for Pt in Urine. Volume 23.

January 31, 2002.

Matrix: Urine
Matrix digestion:
Anticoagulant: Na hep-no effect on concentration
Method: Inductively coupled plasma mass spectrometry ICP-MS

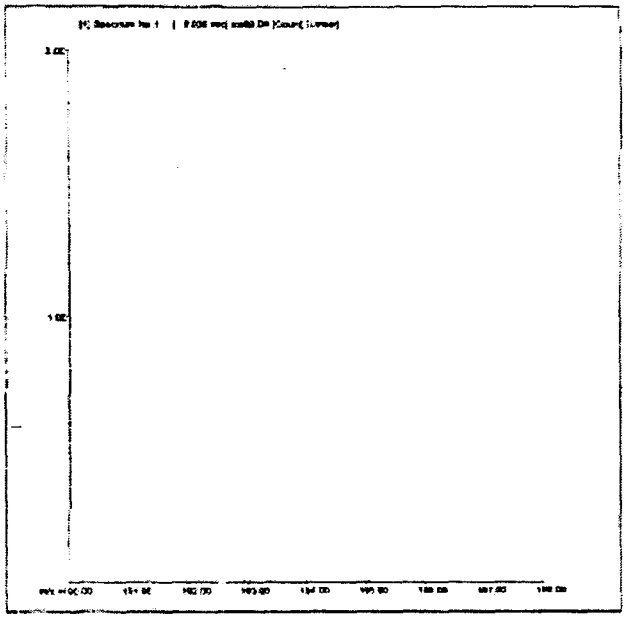
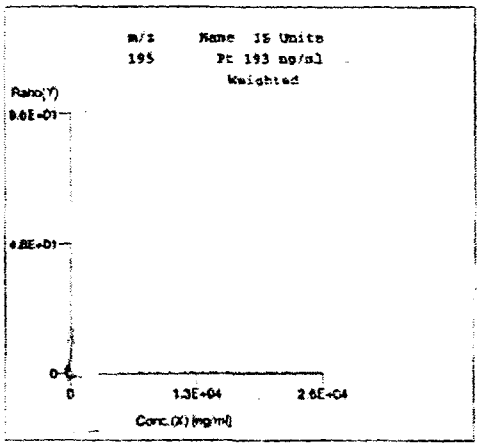


Figure (5.2) 1 - Representative ICP-MS scan of ^{194}Pt, ^{195}Pt and ^{193}Ir in human urine ontaining — ng/mL of platinum (LLOQ) and — ng/mL of iridium internal standard.

Range 100 to 25000 ng/ml (100, 250, 500, 1000, 2500, 5000, 10000 ng/ml)



Lv.	Conc.	Ratio	RSD %
1	100.00	4.66E-1 P	1.42
2	100.00	4.15E-1 P	1.80
3	100.00	4.79E-1 P	9.67E-1
4	250.00	9.58E-1 P	5.60E-1
5	500.00	1.90E+0 P	1.37
6	1000.00	3.83E+0 P	3.34E-1
7	5000.00	1.84E+1 P	3.27
8	1.00E+4	3.67E+1 P	3.43
9	2.50E+4	9.58E+1 A	5.88E-1
10	2.50E+4	9.26E+1 A	4.35E-1
11	2.50E+4	8.95E+1 A	1.13E-1
*12	---	---	---
*13	---	---	---
*14	---	---	---
*15	---	---	---
*16	---	---	---
*17	---	---	---
*18	---	---	---
*19	---	---	---
*20	---	---	---

CurveFit : Y=aX+b

Y = 3.600E-3*X +9.650E-2
X = 2.778E+2*Y -2.681E-1

MinConc: 0.00

Figure (5.2) 2 - Representative calibration curve for the quantification of platinum in human urine

LOQ — ng/ml
Blanks: 6 different lots of human urine.

Accuracy and precision

Nominal amount (ng/mL)	Mean calculated amount (ng/mL)	Percent Accuracy (95% CI)	Within-run Percent Precision (95% CI)	Between-run Percent Precision (95% CI)	Total Percent Precision (95% CI)
100	94.5	-5.49 (-9.56, 1.42)	1.68 (1.21, 2.78)	3.98 (2.35,10.0)	4.32 (2.90, 10.2)
250	240	-4.15 (-7.33, 0.97)	2.05 (1.47, 3.38)	2.93 (1.45, 7.65)	3.57 (2.56, 7.94)
1000	1000	0.23 (-1.28, 1.74)	1.02 (0.73, 1.68)	1.31 (0.58, 3.46)	1.66 (1.20, 3.62)
25000	24300	-2.98 (-4.72, 1.23)	1.15 (0.82, 1.89)	1.58 (0.76, 4.15)	1.95 (1.40, 4.32)

Dilution: up to 10000 ng/ml when diluted.

Nominal Concentration (ng/mL)	25000	100000
Dilution	1:2 (12500 ng/mL)	1:4 (25000 ng/mL)
Calculated concentration (ng/mL)		
Mean	12700	26300
%CV	2.42	0.667
M%D	1.87	5.07

Stability:
Storage: at least
Freeze thaws: from previous assay, 3 cycles were acceptable. Deemed acceptable.
Frozen: at - from previous assay. Deemed acceptable
Benchtop: current study up to 24 and hrs compared to frozen calibration curve.

Table (3.6) 1 - Summary of the stability of platinum at room temperature in human urine

Stability assessment		Concentration (ng/mL)	
		250	25000
24 h stability	Mean	245	25400
	%CV	1.17	0.690
	M%D	-2.07	1.47
48 h stability	Mean	235	25400
	%CV	2.03	0.610
	M%D	-6.20	1.60

Table (3.7) 1 - Summary of processed sample stability data for the assay of platinum in human urine

Stability assessment		Concentration (ng/mL)			
		250[a]	25000[a]	250[b]	25000[b]
48 h stability	Mean	255	25600	251	23800
	%CV	7.85	3.64	7.35	3.70
	M%D	2.10	2.40	0.256	-4.80
168 h stability	Mean	244	23900	259	25200
	%CV	1.94	2.57	1.92	2.69
	M%D	-2.50	-4.60	3.76	0.667

[a]analysed against a freshly processed calibration curve
[b]analysed against a calibration curve processed at the same time as the samples

carry-over

Carry-over determination	25000 ng/mL	100 ng/mL	100 ng/mL
Mean	25100	113	110
%CV	1.28	3.33	5.92
M%D	0.400	13.2	10.3

CrossValidation

2. Oxaliplatin and commercial Pt

Nominal Concentration (ng/mL)	Platinum Source	Mean Concentration (ng/mL)	Estimated Ratio	90% CI for Ratio
250	Platinum Standard	235	NC	NC
	Oxaliplatin	254	1.08	(1.05, 1.11)
25000	Platinum Standard	25400	NC	NC
	Oxaliplatin	25100	0.989	(0.966, 1.01)

NC; parameter not calculated

2 old ICP-MS assay vs. new ICP-MS
?

Problem:

1. No crossvalidation to the old method. Species distinction problem as described before.

SPH0050 Long term storage of Oxaliplatin in human plasma, plasma ultrafiltrate and whole blood.

March 30, 2001.

Assay: validated ICP-MS

Blood: 2, 6, 11 and 22 months
Plasma: 2, 6, 11, 22 and 28 months
Plasma ultrafiltrate: 2, 6,12, 23, and 30 months

Storage: - 20°C

Table 1 Whole Blood

	Pt Concentration (ng/mL)							
	2 months		6 months		11 months		22 months	
Actual Concentration	301	7510	301	7510	301	7510	301	7510
Mean (n=6)	292	7500	304	7670	271	7540	270	7026
CV%	5.78	2.27	1.85	2.99	7.58	3.83	1.65	1.25
M%D	-3.12	-0.24	0.81	2.02	-10.2	0.34	-10.5	-6.45

Table 2 Plasma

	Pt Concentration (ng/mL)									
	2 months		6 months		11 months		22 months		28 months	
Actual Concentration	301	7510	301	7510	301	7510	301	7510	301	7510
Mean (n=6)	260	7560	300	7650	283	7560	283	7374	286	7540
CV%	1.00	0.61	6.46	2.06	9.46	0.36	6.39	2.63	2.02	1.20
M%D	-13.6	0.57	-0.48	1.85	-6.10	0.66	-6.07	-1.81	-5.05	0.40

Table 3 Plasma Ultrafiltrate

	Pt Concentration (ng/mL)									
	2 months		6 months		11 months		23 months		30 months	
Actual Concentration	3.02	200	3.02	200	3.02	200	3.02	200	3.02	200
Mean (n=6)	3.37	186	3.27	190	2.66	201	3.07	201	2.89	199
CV%	5.85	2.30	6.47	2.26	4.31	0.73	6.30	2.42	4.86	1.58
M%D	11.5	-7.21	8.39	-5.14	-11.9	0.39	1.69	0.68	-4.30	-0.55

Conclusion

1. Pt appears stable in
   - Blood for 22 months
   - Plasma for 28 months
   - Plasma ultrafiltrate for 30 months

PKM2983 Oxaliplatin plus 5-FU/LV in GI cancer 85 mg/m2 Vol 5.

October 6, 2000 [redacted]

Single agent Oxaliplatin. Previously untreated colorectal cancer: 12-24% response rate.
Single agent in previous 5-FU treatment, 10% response
Oxaliplatin plus 5-FU/LV in previously treated 25 to30% response rate.

Mechanism: Oxaliplatin forms aquated product (DACH) which then mediates reaction with cellular elements; proteins, DNA (via cross-linking) etc.

Objectives: PK of Oxaliplatin at 85 mg/m2 in combination with 5-FU/LV over 3 cycles in gastrointestinal carcinoma

Secondary: estimate response rate, time to progression and duration of response as well as safety/tolerability.

Study Design

Single center, open-label. Multiple dose study of oxaliplatin by intravenous infusion.

Dosage: 85 mg/m2 over a 2-hr infusion. Concurrent with 300 mg/m2 of continuous 5-FU for 24 weeks.

Formulation: lyophilized powder; 50 to 100 mg of oxaliplatin
Batch: 30 mL 96F13(DPN152) and 50 ml 96F05/1 (DPN154)
Reconstituted in water or 5% glucose for injection.

Dose: BSA (m2) x dose (mg/m2) = dose (mg)

2 hr infusion, once every 14 days.

5-FU infused over 12 weeks at 300 mg/m2

Blood samples: from contralateral side of the infusion. 0, end of infusion, 0.25, 0.5, 0.75, 1, 3, 6, 8, 24 and 48 hrs post-infusion wk1 and wk2.

Urine: 0-24, 24-48.

Plasma ultrafiltrate, plasma, and whole blood. Urine.

Concentration of Pt in Whole Blood BCP

BCP = WBP-[TP(1-HCT)]/HCT

BCP-concentration in blood cells
WBP: concentration in whole blood cells
TP concentration in plasma
HCT defined as 0.44

Pt MW: 195
Oxaliplatin MW: 397

Dose of platinum administered = 195/397 = 0.49

Problems

5-FU regimen differed from safety/efficacy trial. Safety efficacy trial used de Gramont regimen (bolus LV/5-FU followed by 22 hr infusion of 5-FU)

Study. No LV, continuous 5-FU for 12 weeks.

BCP-used fixed hematocrit for all; HCT differs /patient changes with therapy.

Cl= dose/AUC
Vss=CLx MRT

Urinary elimination: CL = Ae0-48/AUC0-48

Patients

9, caucasian, 39 to 71 yrs mean 56; 2 patients had fewer than 3 cycles, therefore, apparently, no data reported. One patient was administered 100 mg/m2 for multiple cycles. Data apparently not reported.

Concomitant
Corticosteroids, 5-HT antagonists and antispasmodics

Results

Table (8.2.1) 1 - Summary of Platinum Pharmacokinetic Parameter Estimates in Plasma Ultrafiltrate, Plasma, Blood Cells and Whole Blood Following Multiple Doses of Oxaliplatin at 85 mg/m^2 q2w

Matrix	C_{end} (µg/mL)	C_{max} (µg/mL)	AUC_{0-48} (µg/mL.h)	AUC (µg/mL.h)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	V_{ss} (L)	CL (L/h)	CL_{ss-ss} (L/h)
Ultrafiltrate										
Mean	0.814	0.814	4.19	4.68	0.434	16.8	391	440	17.4	6.86
SD	0.193	0.193	0.647	1.40	0.347	5.74	406	199	6.35	2.45
Plasma										
Mean	2.03	2.12	47.2	123	0.471	19.3	281	NA	0.687	NA
SD	0.344	0.319	5.10	49.0	0.350	4.96	99.6	NA	0.368	NA
Blood Cells [a]										
Mean	2.64	2.71	105	624	NA	NA	NA	NA	NA	NA
SD	0.591	0.482	17.8	159	NA	NA	NA	NA	NA	NA
Blood										
Mean	2.29	2.31	72.5	257	0.806	21.3	771	NA	0.276	NA
SD	0.156	0.148	6.91	31.3	0.583	5.34	183	NA	0.0755	NA

NA: Not applicable
Mean AUC_{0-ss}, C_{ss}, and C_{max} values were determined on Cycle 3.
Mean AUC, V_{ss}, CL, and CL_{ss-ss} values were determined on Cycle 1.
C_{end}, C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis.
$t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined by compartmental analysis (Cycles 1-3 combined).
[a] Platinum levels in blood cells derived from values in whole blood using a nominal hematocrit of 0.44.
REF: Appendix 6.2.3

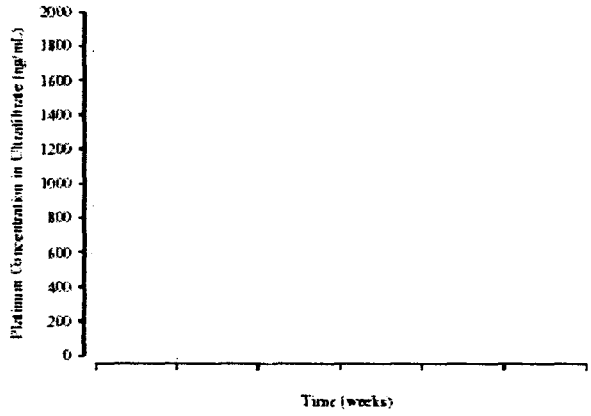


Figure (8.2.1) 4 - Multiple Dose Pharmacokinetics of Platinum in Ultrafiltrate Showing Lack of Accumulation Following a 2 h Infusion of Oxaliplatin at 85 mg/m^2 q2w (n = 6)

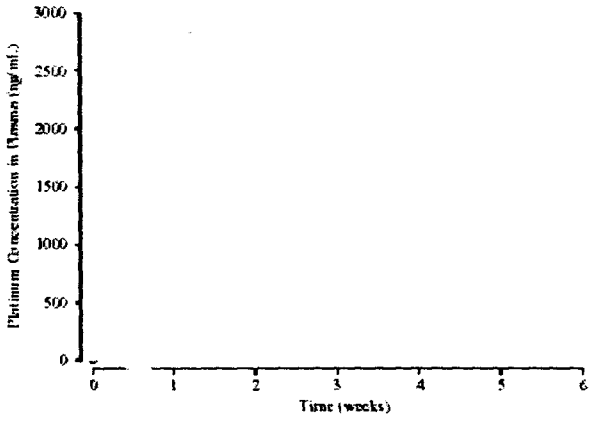


Figure (8.2.1) 5 - Multiple Dose Pharmacokinetics of Platinum in Plasma Showing Accumulation Following a 2 h Infusion of Oxaliplatin at 85 mg/m^2 q2w (n = 6)

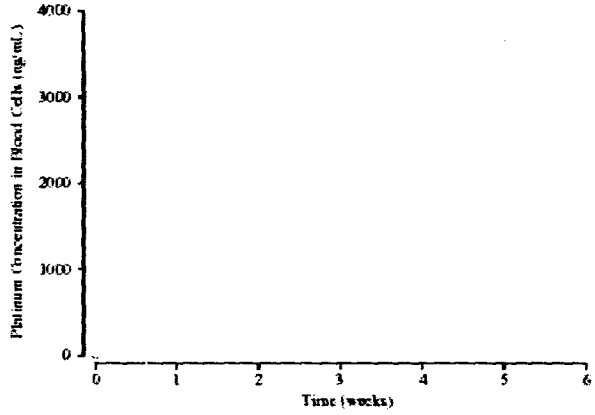


Figure (8.2.1) 6 - Multiple Dose Pharmacokinetics of Platinum in Blood Cells Showing Accumulation Following a 2 h Infusion of Oxaliplatin at 85 mg/m^2 q2w (n = 6)

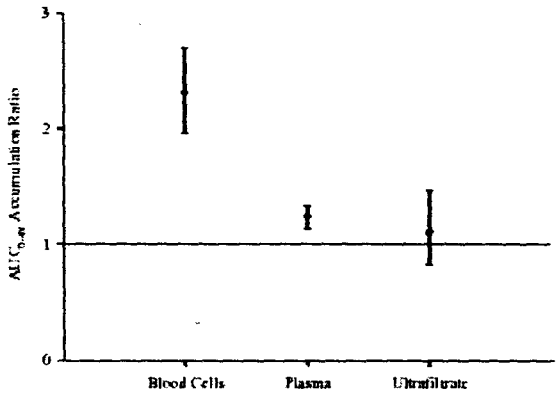


Figure (8.2.2) 2 - Platinum AUC_{0-48} Accumulation Ratios in Plasma, Plasma Ultrafiltrate and Blood Cells (Cycle3/Cycle 1 with 95% Confidence Intervals) Following Multiple Doses of Oxaliplatin at 85 mg/m^2

Table (8.2.2.2.1) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for C_{max} in Plasma

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	1.41	2.18	1.74
23	1.79	1.53	1.72
24	1.82	2.59	2.32
26	1.41	1.69	2.30
27	1.53	1.65	2.17
29	2.64	2.35	2.48
Mean C_{max} (µg/mL)	1.77	2.00	2.12
SD	0.466	0.433	0.319
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	1.22 (0.99, 1.49)		

REF: Appendix 6.2.3

Table (8.2.2.2.2) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for AUC_{0-48} in Plasma

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	39.0	52.3	48.0
23	31.1	37.1	38.5
24	40.3	47.5	48.0
26	37.1	42.5	52.2
27	33.9	44.0	44.4
29	47.8	51.1	51.8
Mean AUC_{0-48} (µg.h/mL)	38.2	45.7	47.2
SD	5.78	5.72	5.10
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	1.24 (1.14, 1.34)		
Cycle 1 vs. Cycle 3	0.807 (0.74, 0.88)		
Cycle 2 vs. Cycle 3	0.969 (0.89, 1.05)		

REF: Appendix 6.2.3

Table (8.2.2.1.1) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for C_{max} in Ultrafiltrate

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	0.411	1.17	0.630
23	0.757	0.305	0.770
24	1.77	0.822	0.643
26	0.865	1.14	0.806
27	N/A	0.743	1.16
29	0.556	0.568	0.877
Mean C_{max} (µg/mL)	0.872	0.790	0.814
SD	0.533	0.332	0.193
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	1.039 (0.57, 1.90)		

REF: Appendix 6.2.3

Table (8.2.2.1.2) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for AUC_{0-48} in Ultrafiltrate

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	2.76	4.67	3.90
23	3.98	3.09	4.37
24	5.24	3.38	3.39
26	4.35	6.65	4.92
27	3.18	3.72	4.91
29	3.60	3.16	3.64
Mean AUC_{0-48} (µg.h/mL)	3.85	4.11	4.19
SD	0.880	1.37	0.647
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	1.10 (0.82, 1.47)		
Cycle 1 vs. Cycle 3	0.909 (0.68, 1.22)		
Cycle 2 vs. Cycle 3	0.953 (0.71, 1.27)		

REF: Appendix 6.2.3

Table (8.2.2.3.1) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for C_{max} in Blood Cells

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	1.54	3.30	3.49
23	2.25	2.19	2.88
24	1.40	1.21	2.23
26	1.92	2.58	2.60
27	1.23	2.10	2.87
29	1.15	2.41	2.20
Mean C_{max} (µg/mL)	1.58	2.30	2.71
SD	0.427	0.683	0.482
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	1.74 (1.32, 2.30)		

REF: Appendix 6.2.3

Table (8.2.2.3.2) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for AUC_{0-24} in Blood Cells

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	52.1	97.5	120
23	50.6	81.5	114
24	31.7	39.4	83.9
26	48.5	93.6	108
27	47.3	73.9	121
29	42.5	69.7	81.5
Mean AUC_{0-24} (ug.h/mL)	45.4	75.9	105
SD	7.52	20.9	17.8
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	2.31 (1.96, 2.71)		
Cycle 1 vs. Cycle 3	0.434 (0.37, 0.51)		
Cycle 2 vs. Cycle 3	0.705 (0.60, 0.83)		

REF: Appendix 6.2.3

Table (8.2.2.4.1) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for C_{max} in Whole Blood

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	1.43	2.67	2.45
23	1.44	1.79	2.23
24	1.63	1.69	2.09
26	1.58	2.08	2.24
27	1.34	1.82	2.47
29	1.58	1.86	2.35
Mean C_{max} (µg/mL)	1.50	1.99	2.31
SD	0.115	0.360	0.148
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	1.54 (1.33, 1.78)		

REF: Appendix 6.2.3

Table (8.2.2.4.2) 1 - Means (±SD) and Ratio of Geometric Means with 95% CI for $AUC_{t=0}$ in Whole Blood

Patient ID	Cycle 1	Cycle 2	Cycle 3
21	44.7	72.2	79.8
23	39.7	56.6	71.6
24	36.5	44.0	63.8
26	42.1	65.0	76.7
27	39.8	57.1	78.3
29	45.5	59.3	64.8
Mean $AUC_{t=0}$ (µg.h/mL)	41.4	59.0	72.5
SD	3.41	9.44	6.91
Ratio of Geometric Means (95% CI)			
Cycle 3 vs. Cycle 1	1.75 (1.58, 1.93)		
Cycle 1 vs. Cycle 3	0.572 (0.52, 0.63)		
Cycle 2 vs. Cycle 3	0.810 (0.73, 0.89)		

REF: Appendix 6.2.3

Table (8.2.3) 1 - Summary of Platinum Renal Clearance and Percentage of the Dose Excreted in the 0-48h interval

Patient	$CL_{R,0-48}$ (L/h)	% Dose Excreted in 48 Hours	% Dose Excreted in 24 Hours
21	11.7	48.4	44.8
23	6.22	28.2	24.0
24	5.41	39.9	35.7
26	6.06	39.4	34.4
27	6.72	24.4	17.6
29	5.04	27.2	17.8
Mean	**6.86**	**34.6**	**29.1**
SD	**2.45**	**9.41**	**11.0**

REF: Appendices 6.2.2.5 and 6.2.3

Efficacy:
1 CR; not verified
1 PR
2 PD

AE

Pat 22: cerebrovascular episode 17 days post; not drug-related
Pat 25: severe anemia and hyponatremia; 24 days post dose; not relatred to drug; died
Pat 27: skin disorder 12 mg dexamathasone; grade 3 infection 118 days post dose. 4 gm ampicillin

Conclusions:

1. No accumulation in ultrafiltrate; slight accumulation in plasma; modest accumulation in whole blood.
2. Renal clearance was about 40% of total Clearance

3. 24-48 % of dose excreted in the urine.

Problems

1. BCP calaculations are questionable due to variations in hematocrit; may have large RBC accumulation.
2. How do PK compare to Oxaliplatin alone?? Oxaliplatin plus De Gramont regimen?

POP7488 Oxaliplatin in patients with impaired renal function. Vol 15

12/6/99 to 6/27/01
NCI-CTEP Chris Takimoto

EU: dosages of 85 mg/m2 q2wks or 130 mg/m2 q3wks.

Study dosage: 130 mg/m2
4 groups, based on renal function
Group A: 12 patients normal renal function
Groups B, C, D, started at different doses and were escalated
A. Normal > 60 ml/min dose: 130 mg/m2
B mild 40 to 59 ml/min dose: 105 to 130 mg/m2
C Moderate 20-39 ml/min dose: 80 to 105 to 130 mg/m2
D severe < 20 ml/min dose: 60 to 80 to 105 to 130 mg/m2

DLT ≥ grade 3 non-hematological or hematological toxicity

Table 6.1-1 Treatment Plan

Group	Creatinine Clearance	Starting Dose of Oxaliplatin and Escalation Plan
A (normal controls)	> 60 mL/min	130 mg/m^2
B (mild dysfunction)	40 to 59 mL/min	105 mg/m^2 130 mg/m^2
C (moderate dysfunction)	20 to 39 mL/min	80 mg/m^2 105 mg/m^2 130 mg/m^2
D (severe dysfunction)	< 20 mL/min	60 mg/m^2 80 mg/m^2 105 mg/m^2 130 mg/m^2

Cockcroft-Gault

CLcr (ml/min) = [(140-Age in yrs) x weight in kg]/72 x serum Cr in mg/ml

THIS IS FOR MALES!

Patients: 37 patients enrolled. Groups a-C were fulfilled, group D had only 1 patient.

Table 7.1-1 Patient Enrollment by Treatment Group and Dose Cohort

Group	Group A normal controls	Group B mild dysfunction		Group C moderate dysfunction			Group D severe dysfunction
CrCl	> 60 mL/min	42 – 59 mL/min		20 – 39 mL/min			< 20 mL/min
Starting dose of oxaliplatin	130 mg/m^2	105 mg/m^2	130 mg/m^2	80 mg/m^2	105 mg/m^2	130 mg/m^2	60 mg/m^2
Number of patients	12	3	7	3	3	8	1

Table 8.2-1 Patient Demographics by Study Group and Treatment Cohort[a]

Characteristic	Group A normal controls	Group B mild dysfunction		Group C moderate dysfunction			Group D severe dysfunction	Total
CrCl	> 60 mL/min	42 – 59 mL/min		20 – 39 mL/min			< 20 mL/min	
Starting dose of oxaliplatin	130 mg/m^2	105 mg/m^2	130 mg/m^2	80 mg/m^2	105 mg/m^2	130 mg/m^2	60 mg/m^2	
Number of patients	12	3	7	3	3	8	1	37
Median Age (range)	56 (41 – 72)	66 (54-77)	70 (32 – 78)	63 (31 – 86)	64 (52 – 78)	69 (47 – 76)	82	64 (33 – 86)
Gender (Number and %)								
Male	8 (67%)	1 (33%)	5 (71%)	1 (33%)	2 (67%)	5 (63%)	1 (100%)	23 (62%)
Female	4 (33%)	2 (67%)	2 (29%)	2 (67%)	1 (33%)	3 (37%)		14 (38%)
Mean weight (kg) ± STD (range)	78.5 ± 29.7 (55 – 165)	61.9 ± 25.9 (40 – 90)	68.8 ± 11.5 (56 – 92)	58.3 ± 8.0 (49 – 64)	69.4 ± 17.8 (50 – 85)	90.4 ± 18.0 (6; – 114)	60.5	74.6 (40 – 165)
Ethnicity (Number and %)								
White	10 (83%)	2 (67%)	3 (43%)	1 (33%)	2 (67%)	7 (88%)	1 (100%)	26 (70%)
Black	2 (17%)	0	2 (29%)	2 (67%)	0	0	0	6 (16%)
Hispanic	0	0	0	0	0	1 (12%)	0	1 (3%)
Asian	0	1 (33%)	0	0	0	0	0	1 (3%)
Pacific Islander	0	0	0	0	1 (33%)	0	0	1 (3%)
Unknown	0	0	2 (29%)	0	0	0	0	2 (5%)

continued

Plasma, ultrafiltrate and urine samples.

Sample collection: 0, 2, 2,25, 2,5, 2,75, 3, 5, 8, 24, and 48, 1 wk, 2 wks and 3 wks, In cycles 1 and 2.

Urine collected from 0-24 and 24-48 hrs
Clr = AmtPt/AUC0-48
AmtPt is the total amount of Pt excreted in urine from 0-48 hrs
AUC0-48 is plasma ultrafiltrate over 0-48 hrs

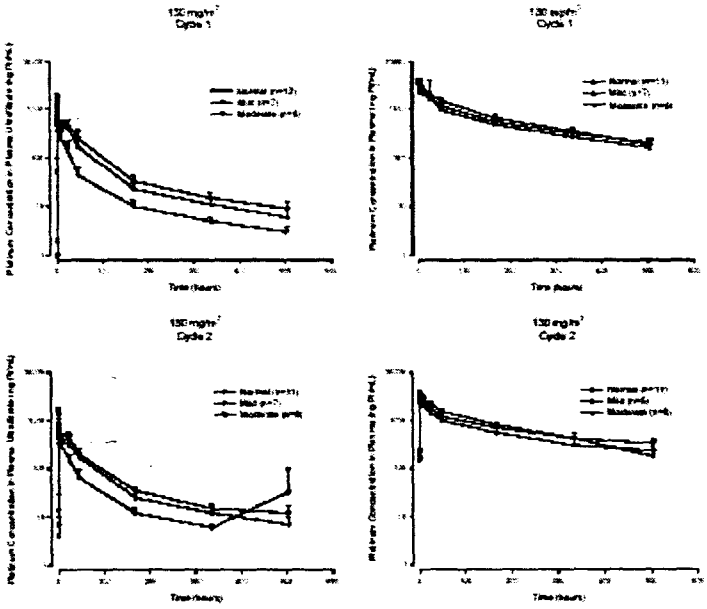


Table (7.3) 1 - Summary of Mean Model Derived Half Lives of Platinum in Plasma-Ultrafiltrate

Renal status	t1/2 α, hrs (SD)	t1/2 β, hrs (SD)	t1/2 γ, hrs (SD)
Normal (n=9)	0.205 (0.079)	15.0 (4.2)	327 (260)
Mild (n=3)	0.157 (0.059)	25.4 (9.1)	370 (313)
Moderate (n=9)	0.166 (0.053)	40.9 (12.3)	511 (275)
Severe (n=1)	0.222 (NA)	68.1 (NA)	286 (NA)

NA Not applicable

Table (7.3) 2 - Summary of Mean Non-Compartmental Pharmacokinetic Parameters of Platinum in Plasma-Ultrafiltrate

Cycle	Renal status	Dose (mg/m²)	No. of Subject	Cmax (µg Pt/mL)	AUC0-∞ (µg Pt .h/mL)	AUC0-last (µg Pt .h/mL)	Vss (L)	Cl (L/h)
1	Normal	150	11	1.51 (0.198)	9.15 (2.74)	26.4 (5.02)	603 (369)	7.91 (2.46)
	Mild	105	3	0.841 (0.562)	13.4 (3.46)	32.7 (16.2)	385 (234)	3.07 (1.45)
		130	6	1.31 (0.514)	17.4 (3.49)	39.7 (13.5)	256 (72.4)	3.04 (0.807)
	Moderate	80	1	0.634 (0.363)	15.3 (0.337)	29.5 (NA)	167 (NA)	2.22 (NA)
		105	2	1.45 (0.226)	19.1 (0.446)	42.0 (1.25)	199 (33.9)	2.45 (0.121)
		130	5	1.39 (0.576)	20.5 (5.05)	44.6 (14.6)	303 (146)	3.37 (1.79)
	Severe	60	1	0.716 (NA)	9.67 (NA)	32.2 (NA)	241 (NA)	1.63 (NA)
2	Normal	150	9	1.56 (0.324)	9.79 (1.46)	28.2 (9.65)	977 (698)	6.04 (2.15)
	Mild	105	2	1.13 (0.451)	11.9 (3.49)	26.8 (1.06)	588 (124)	3.26 (0.725)
		130	5	1.49 (0.311)	15.5 (5.78)	40.5 (13.1)	259 (168)	3.03 (0.917)
	Moderate	80	3	0.660 (0.0838)	12.7 (3.02)	30.1 (7.11)	187 (174)	2.08 (0.307)
		105	1	0.728 (NA)	12.3 (NA)	25.1 (NA)	301 (NA)	3.96 (NA)
		130	5	1.61 (0.207)	22.3 (7.47)	48.8 (13.4)	227 (105)	2.84 (1.06)
	Severe	60	1	0.656 (NA)	6.89 (NA)	25.6 (NA)	244 (NA)	2.06 (NA)

NA = not applicable

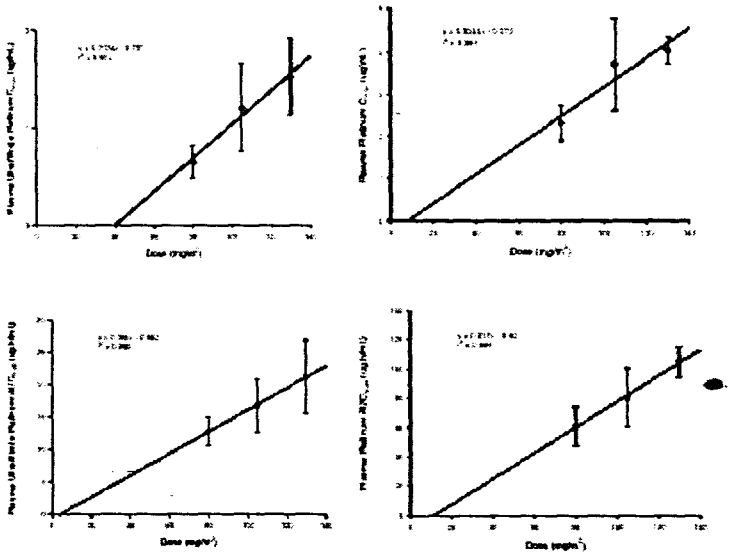


Figure (7.3) 1 - Relationships Between Oxaliplatin Dose and Plasma Ultrafiltrate (left hand panels) or Plasma (right hand panels) Platinum C_{max} (upper panels) or AUC_{0-48} (lower panels) Values in Moderately Renal Impaired Patients

Table (7.4) 1 - Summary of Mean Model Derived Half Lives of Platinum in Plasma

Renal status	t1/2 α, hrs (SD)	t1/2 β, hrs (SD)	t1/2 γ, hrs (SD)
Normal n=(11)	0.345 (0.260)	22.0 (10.4)	260 (182)
Mild n=(8)	0.401 (0.452)	22.9 (9.0)	351 (305)
Moderate n=(10)	0.283 (0.251)	22.7 (10.2)	224 (151)
Severe n=(1)	0.178 (NA)	30.0 (NA)	451 (NA)

Table (7.4) 2 - Summary of Mean Non-Compartmental Pharmacokinetic Parameters of Platinum in Plasma

Cycle	Renal Status	Dose (mg/m²)	No. of Subjects	C_{max} (µg Pt/mL)	$AUC_{0-\infty}$ (µg Pt.h/mL)	AUC (µg Pt.h/mL)	Vss (L)	Cl (L/h)
1	Normal	130	19	3.94 (1.533)	89.5 (45.3)	315 (70.2)	73.9 (21.9)	0.413 (0.154)
	Mild	105	3	3.32 (1.22)	57.3 (23.9)	270 (83.8)	79.6 (46.2)	0.338 (0.0417)
		130	6	3.63 (0.367)	83.3 (12.4)	342 (26.0)	67.7 (29.5)	0.294 (0.0214)
	Moderate	80	2	2.31 (0.629)	65.2 (0.358)	267 (23.4)	51.4 (22.0)	0.241 (0.0138)
		105	2	3.60 (1.87)	80.5 (19.7)	233 (58.5)	53.9 (15.0)	0.458 (0.136)
		130	5	4.10 (0.4323)	104 (10.55)	416 (58.4)	64.4 (17.9)	0.318 (0.0556)
	Severe	60	1	1.76 (NA)	42.6 (NA)	198 (NA)	76.4 (NA)	0.265 (NA)
2	Normal	130	8	3.35 (0.488)	74.6 (11.2)	332 (83.1)	77.8 (19.9)	0.367 (0.141)
	Mild	105	2	2.64 (0.389)	68.6 (6.17)	350 (41.6)	74.2 (16.2)	0.249 (0.0356)
		130	5	3.53 (0.672)	85.9 (21.2)	395 (81.7)	63.2 (25.8)	0.296 (0.0695)
	Moderate	80	3	2.46 (0.336)	65.6 (12.2)	269 (70.5)	43.7 (9.56)	0.240 (0.0583)
		105	1	3.08 (NA)	70.4 (NA)	241 (NA)	71.5 (NA)	0.413 (NA)
		130	5	3.97 (0.139)	106 (11.6)	470 (51.2)	64.6 (10.2)	0.288 (0.0465)
	Severe	60	1	1.30 (NA)	48.0 (NA)	214 (NA)	49.0 (NA)	0.245 (NA)

NA= not applicable

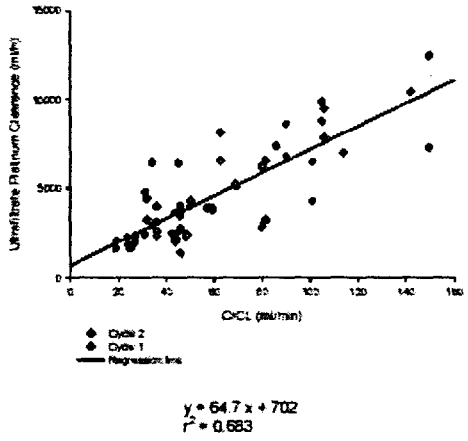


Figure (7.5) 1 - Relationship Between Ultrafiltrate Platinum Clearance and CrCL

Conclusions:

1. renal function: no effect on Cmax or alpha or gamma t1/2 for ultrafiltratesignificant decrease in ultrafiltrae Pt Cl, and significant increase in bt1/2 and AUC with renal impairment
2. no increase in toxicity.
3. Upt CL was correl;ated with Clcr
4. 40 % renal excretionin normals, 20% in moderate.proptotional to dose.

5. No reduction warranted. With mild/moderate impairment.

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