CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-759

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-759 (Original NDA #21-492)**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**03/31/04**
PRODUCT:	**Eloxatin (Oxaliplatin)**
INTENDED CLINICAL POPULATION:	**Advanced colorectal cancer**
SPONSOR:	**Sanofi Synthelabo Pharmaceuticals, Inc.**
DOCUMENTS REVIEWED:	**Electronic submission**
REVIEW DIVISION:	**Division of Oncology Drug Products (HFD-150)**
PHARM/TOX REVIEWER:	**Margaret E. Brower, Ph.D.**
PHARM/TOX SUPERVISOR:	**John Leighton, Ph. D.**
DIVISION DIRECTOR:	**Richard Pazdur, M.D.**
PROJECT MANAGER:	**Christy Cottrell**

Date of review submission to Division File System (DFS): 07/12/04

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: approval (see below)

B. Recommendation for nonclinical studies:
Non-clinical studies for the Oxaliplatin lyophilized formulation were reviewed with the original IND (#41-817) and NDA [redacted] #21,492), and supported approval for the treatment of advanced colorectal cancer in combination with 5-FU based therapy. The current formulation change to the Oxaliplatin aqueous solution is consistent with previous approval.

The bridging study submitted to qualify formulation change can also be used to qualify the degradation product, [redacted]

C. Recommendations on labeling: No additional preclinical labeling recommendations at this time

II. Summary of nonclinical findings

A. Brief overview of non-clinical findings

The approved lyophilized formulation of oxaliplatin [redacted] which is reconstituted in 5% dextrose at a concentration of 5mg/mL oxaliplatin.

A bridging study was conducted comparing the toxicity of the lyophilized formulation to 3 oxaliplatin solution formulations including:
1- an aqueous formulation [redacted]
2- [redacted]

3- an oxalic acid formulation [redacted]

The toxicity of oxaliplatin in the aqueous solution formulation is similar to the toxicity observed with the lyophilized formulation, originally approved with NDA #21,492. [redacted]

[redacted]

Oxalic acid was identified as a biotransformation product of oxaliplatin and was examined for its ability to improve stability of the drug. The formulation of oxaliplatin in the oxalic acid solution exhibited increased toxicity. [redacted]

B. Pharmacologic activity
No change from original NDA.

C. Nonclinical safety issues relevant to clinical use
The toxicity of oxaliplatin in the aqueous solution formulation is similar to the toxicity of the currently marketed product formulation.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

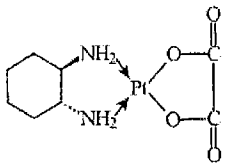
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-759
Review number: 1
Sequence number/date/type of submission: 000/March 31, 2004 /NDA
Information to sponsor: Yes ( ) No (X)
Sponsor: Sanofi Pharmaceuticals, Inc, Malvern, PA
Manufacturer for drug substance: [redacted]

Reviewer name: Margaret E. Brower, Ph.D.
Division name: Division of Oncology Drug Products
HFD #: 150
Review completion date: July 6, 2004

Drug:

Trade name: Eloxatin
Generic name: Oxaliplatin
Code name: SR96669, L-OHP, 1-OHP, NSC-266046, NSC-271670, JM-83, PR 54780, 1670 RB7
Chemical name: cis-[(1R,2R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)-O,O]platinum 1,2-diaminocyclohexane (DACH)
CAS registry number: 61825-94-3
Molecular formula/molecular weight: $C_8H_{14}N_2O_4Pt$/397.3
Structure:



Relevant INDs/NDAs/DMFs: IND 41,817, [redacted], 21,492

Drug class: Platinum derivative

Intended clinical population: First-line treatment of advanced colorectal cancer in combination with 5 FU-based therapy

Clinical formulation: Commercial products are supplied as 50mg and 100mg vials. Lyophilized oxaliplatin is a freeze-dried powder which is reconstituted in water or 5% glucose. Comparative composition of the 100mg formulations follows.

	Oxaliplatin solution formulation	Lyophilized formulation (original NDA)
Oxaliplatin (a.i.)	100mg	100mg
[redacted]		
Water q.s. (solvent)		
Dilution		

Route of administration: iv

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:
TXA0551 A single-dose intravenous toxicity study in mice with lyophilized and solutions formulations of oxaliplatin

Studies not reviewed within this submission: none

2.6.2 PHARMACOLOGY REFER TO NDA 21,492

2.6.2.1 Summary Refer to NDA 21,492
2.6.2.2 Primary pharmacodynamics No additional studies
2.6.2.3 Secondary pharmacodynamics No additional studies

2.6.2.4 Safety pharmacology

Refer to NDA 21,492 for specific study data. Oxaliplatin produced ventricular fibrillation and death in dogs administered single dosages of $\geq$150mg/m^2. Cardiac toxicity was not detected in cardiotoxicity studies conducted in rats or monkeys, suggesting that either the dog is more sensitive than other species or that the cardiotoxicity may be species specific. Nephrotoxicity was observed in rats at doses of $\geq$9mg/m^2. Oxaliplatin has a lower potential to produce myelosuppression compared to carboplatin, but is similar to cisplatin in this regard. Oxaliplatin is neurotoxic, significantly depressing neuronal cells *in vivo*. No additional studies submitted.

2.6.2.5 Pharmacodynamic drug interactions

No additional studies submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY Refer to NDA 21,492

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Refer to NDA 21,492 for specific study data. Pharmacokinetics/toxicokinetics were conducted in mice and dogs. Systemic exposure and half-life (10-120h) of oxaliplatin was consistent in plasma and whole blood fraction in dogs; however, in mice half-life was 49m and exposure was 1350-2875-fold higher when normalized to dose. However, different assay methods were used in determining oxaliplatin concentrations in dogs and mice (more specific assay methods used for dog studies), and species differences were likely due to methodology. No additional studies submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Refer to NDA 21,492

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:
Refer to IND 41,817 and [redacted] 21,492 for specific study data. Single dose studies were performed in mice (iv, ip), rats (iv, ip, oral) and dogs (iv) with the lyophilized formulation. Oxaliplatin was found to cause hepatic toxicity in rats. In dogs, target organs included the heart (cause of mortality), GI tract, liver and kidney. The STD_{10} in mice was 84-172mg/m^2 iv and 114-138mg/m^2 iv in rats. The HNSTD in dogs was 150mg/m^2. Repeat dose studies were conducted iv in rats, dogs and baboon. Oxaliplatin produced myelosuppression, and dose-related renal necrosis in rats at 6mg/m2 dosed daily x 3, q21d x 3cycles. In dogs, significant cardiac toxicity was observed (ventricular extrasystole and filbrillation in EKG, death due to cardiac failure), as well as toxicities of the kidney (degeneration of renal tubules), nervous system (tremors, trembling, shaking, unsteady gait), liver, testes (atrophy, hypoplasia), and GI tract; the HNSTD was 35-45mg/m2 dosed daily x 5 q28d up to 6cycles. The lethal doses were 40 (6cycles) and 60 (1cycle) mg/m^2/day.

The approved lyophilized formulation of oxaliplatin is described as a lyophilsate (water removed during lyophilization) which is reconstituted in 5% dextrose at a concentration of 5mg/mL oxaliplatin.

A bridging study was conducted comparing the toxicity of the lyophilized formulation to 3 oxaliplatin solution formulations including:

1-an aqueous formulation [redacted]
2- [redacted]
3-an oxalic acid formulation [redacted]

The single-dose bridging study indicated that the toxicity of oxaliplatin in the aqueous solution formulation is similar to the toxicity observed with the lyophilized formulation, originally approved with NDA #21,492.

Genetic toxicology:
Refer to IND 41,817 for specific study data. Oxaliplatin was negative in the Ames test, but was positive in all other genotoxicity tests, i.e., mouse lymphoma assay for mammalian cells (TK locus), mouse micronucleus assay, and chromosome aberration assay for human lymphocytes. Oxaliplatin was mutagenic and clastogenic both in the presence or absence of metabolic activation. The relative mutagenicity and clastogenicity was comparable to that of cisplatin as indicated in the original NDA.

Carcinogenicity: Carcinogenicity studies were not performed.

Reproductive toxicology:
The fertility index was not depressed following dosing of Oxaliplatin to rats; however, developmental mortality (post-implantation loss/resorption) was complete at the HD (12mg/m^2). In addition, repeat-dose studies in rats and dogs revealed atrophy and hypoplasia of the testis. Oxaliplatin was embryotoxic and fetotoxic (decreased fetal weights, delayed ossification) in rats.

No external, visceral, or skeletal malformations were observed in rats or rabbits. However, these findings may have been the result of complete fetal mortality in the rat prior to observation of structural alteration, and inadequate doses administered to rabbits.

Special toxicology: See notations under Safety Pharmacology.

2.6.6.2 Single-dose toxicity
[Data submitted to support formulation change]

Study title: A single-dose intravenous toxicity study in mice with lyophilised and solution formulations of oxaliplatin

Key study findings:
• Toxicity of oxaliplatin in aqueous solution formulation similar to toxicity of lyophilized formulation
•

Study no.: FSRFU-TXA0551-EN-E01
Volume #, and page #: electronic submission; p. 1/199
Conducting laboratory and location: Sanofi-Synthelabo Research
Date of study initiation: November 23, 1999
GLP compliance: GLP compliant with exception of serum analysis
QA report: yes (X) no ( )
Drug, lot #, and % purity: [purity not provided]
4 solutions tested:
1- Lyophilsate reconstituted at 5mg/mL oxaliplatin in 5% dextrose (batch 98-01783)
2- Solution containing 5mg/mL oxaliplatin in 0.2mM oxalic acid solution (batch ALW-6237-138; (biotransformation product of oxaliplatin examined for its ability to improve stability of the drug)
3- Solution containing 5mg/mL oxaliplatin in water (lot BJK101999F&G) (aqueous solution formulation)
4-

Vehicle: 5% dextrose for lyophilized formulation, aqueous formulation, and impurity solution; 0.2mM oxalic acid diluted in 5% dextrose for oxalic acid formulation

Methods
Doses: 0, 12.5, 15, 17.5, 20mg/kg (37.5, 45, 49.5, 60mg/m^2) [12.5mg/kg dose for all formulations adminstered 8d following administration of higher doses in order to accommodate necropsy schedule]

Species/strain: mice/[redacted]:CD-1 (ICR) BR
Number/sex/group: 10♀
Route, formulation, volume, and infusion rate: iv, volume 10mL/kg
Satellite groups: none
Age: 7-8w and 8-9w (12.5mg/kg group)
Weight: 24-31g and 24-34g (12.5mg/kg group)
Treatment duration: single dose
Unique study design or methodology: none

Observations

Mortality (daily)	See table below
Clinical observations (30m, 1, 1.5, 2, 4, 6h/day of dosing, 2X daily thereafter)[a]	Premature decedents: 12.5mg/kg: piloerection, hunched posture, pale extremities, lethargy, emaciation, partially closed eyes 17.5-20mg/kg: piloerection, hunched posture, labored breathing, hypothermic, lethargy, emaciation, prostration, tremors, loss of hindlimb extension, unsteady gait, partially closed/dark eyes, anal staining Surviving animals: 12.5mg/kg: tail discoloration, skin encrustation, piloerection, hunched posture 15mg/kg: convulsions (2/10 oxalic acid formulation w/30' recovery), piloerection, hunched posture, tail lesions, emaciation, dark eyes, pale extremities [progressive clinical signs d2-d14 (some recovery d14)] 17.5-20mg/kg: similar to decedents, some recovery by d14: piloerection, hunched posture, tail lesions
Body weights (predosing, d2, 8, 14)	See table below
Necropsy (d15 if not premature decedent)	See gross pathology
Gross pathology (full macroscopic examination indicated; individual tissues not indicated)	

[a] Similar findings all formulations

Premature decedents

Formulation	Dose (mg/kg)	# of deaths	Time of death/status
Lyophilized	12.5	0/10	
	15	0/10	
	17.5	3/10	d8/1FD; d9/2FD
	20	8/10	d8/1SM; d9/2SM, 2FD; d10/1SM; d13/2SM
Solution 1 (oxalic acid)	12.5	2/10	d11/1FD; d14/1FD
	15	0/10	
	17.5	3/10	d9/1SM, 2FD
	20	9/10	d8/2SM, 1FD; d9/2SM, 2FD; d10/1SM; d13/1SM
Solution 2 (aqueous)	12.5	0/10	
	15	0/10	
	17.5	2/10	d9/1FD; d12/1SM
	20	9/10	d8/3SM, 3FD; d9/1SM, 1FD; d10/1SM

Solution 3 (degradate)	12.5	0/10	
	15	0/10	
	17.5	2/10	d9/1SM, 1FD
	20	6/10	d9/2SM, 2FD; d10/1FD; d11/1SM

FD=found dead; SM= sacrificed moribund

Percent mean BW loss: day 8 compared to day 1[a]

Formulation	Doses (mg/kg)			
	12.5	15	17.5	20
Lyophilized	10	5	13	19
Formulation 1	5	11	18	22
Formulation 2	4	11	13	23
Formulation 3	7	8	18	22

[a]Some BW recovery by d14

Gross pathology – Premature decedents (N specified/group)

Organ/finding	Lyophilized (mg/kg)		Oxalic acid (mg/kg)			Aqueous (mg/kg)		Degradate (mg/kg)	
	17.5	20	12.5	17.5	20	17.5	20	17.5	20
Stomach/distended	1/3	1/8			2/9		3/9		2/6
/impacted	1/3				1/9		3/9		2/6
/prominent vasculature, dark contents					1/9				
Ileum/distended	3/3	7/8		3/3	7/9	2/2*	7/9	2/2	3/6
/red discoloration	3/3	7/8		3/3	8/9	1/2	9/9	2/2	6/6
/gaseous distention					1/9				
Jejunum/distended				1/3	2/9		1/9	1/2	
Cecum/gaseous distention					1/9	1/2	1/9		
Duodenum/distended, dark contents					1/9				
Liver/pale					2/9		1/9		
Kidneys/pale		2/8			1/9				

* Noted incidence of 1/2 in summary table; 2/2 in tabulated gross necropsy

Gross pathology – Scheduled sacrifice (N specified/group)

Organ/finding	Control	Lyophilized (mg/kg)		Oxalic acid (mg/kg)			Aqueous (mg/kg)		Degradate (mg/kg)	
		17.5	20	15	17.5	20	17.5	20	17.5	20
Cecum/gaseous distention	1/10			2/10	2/7		1/8*			

*incidence 2/10 at 15mg/kg aqueous and 3/10 at 15mg/kg degradate

Additional finding: spleen increased in size in 4/10 12.5mg/kg degradate females

Study conclusions:
- Lyophilized formulation STD_{30} = 17.5mg/kg (52.5mg/m^2)
- Oxalic acid formulation STD_{20} = 12.5mg/kg (37.5mg/m^2)
- Water formulation STD_{20} = 17.5mg/kg (52.5mg/m^2)
- [redacted]
- Multiple clinical observations all formulations, decrease in BW at 17.5 and 20mg/kg
- Primary gross pathology findings premature decedents (17.5 and 20mg/kg): distention and discoloration of stomach and ileum
- Toxicity of oxaliplatin in aqueous formulation similar to toxicity of lyophilized formulation
- [redacted]

2.6.6.3 Repeat-dose toxicity No additional studies submitted
2.6.6.4 Genetic toxicology No additional studies submitted
2.6.6.5 Carcinogenicity No studies submitted
2.6.6.6 Reproductive and developmental toxicology No additional studies submitted
2.6.6.7 Local tolerance No studies submitted
2.6.6.8 Special toxicology studies No studies submitted
2.6.6.9 Discussion and Conclusions See below
2.6.6.10 Tables and Figures See study data tabulated above

2.6.7 TOXICOLOGY TABULATED SUMMARY See below

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
The toxicity of oxaliplatin in the aqueous solution formulation is similar to the toxicity of the currently marketed product formulation.

The toxicity of the aqueous solution containing the degradation product, [redacted] is similar to the toxicity observed with the aqueous formulation alone; this study can be used to qualify the degradate/impurity.

Unresolved toxicology issues: none

Recommendations: Approval for change in formulation to the aqueous solution

Suggested labeling: No recommended changes in preclinical labeling

Signatures:

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes _X__ No ___

APPENDIX/ATTACHMENTS: NONE

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/s/

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7/12/04 09:33:37 AM
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