DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 22 2000

TRANSMITTED VIA FACSIMILE

Mark Moyer
Director
Regulatory Affairs
Sanofi-Synthelabo, Inc.
9 Great Valley Parkway
Malvern PA 19355

RE: NDA[ ]
Eloxatin (oxaliplatin)
MACMIS ID # 9076

Dear Mr. Moyer:

The Division of Drug Marketing, Advertising, and Communications (DDMAC), as part of its routine surveillance program, has received information that pre-approval promotional activities for Eloxatin (oxaliplatin) have been conducted by Sanofi-Synthelabo, Inc. (Sanofi) in violation of the Federal Food, Drug, and Cosmetic Act (the Act), and regulations promulgated thereunder. Specifically, Sanofi disseminated promotional materials about Eloxatin, an investigational drug, that suggest that it is effective for treating different types of cancer. Section 312.7 of title 21 of the Code of Federal Regulations (C.F.R.) specifically states that a "sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational drug is safe or effective for the purposes for which it is under investigation."

At the May 19-23, 2000, meeting of the American Society of Clinical Oncology ("ASCO") in New Orleans, LA, Sanofi had a booth in the commercial area where Sanofi representatives distributed material that promoted Eloxatin for use in the treatment of solid tumors. For example, the slide kit entitled, "Oxaliplatin -- A Novel Compound Under Investigation for the Treatment of Solid Tumors" included conclusory statements such as:

". . . oxaliplatin is active against several cisplatin-resistant cell lines, colon carcinoma, and other solid tumors that are not responsive to cisplatin."

"[results from colon cell line studies] support the clinical indication of 5-FU plus oxaliplatin in the treatment of colon carcinoma."

"In vivo antitumor studies were conducted with oxaliplatin in combination with CPT-11, cyclophosphamide [ ], mitomycin-C, carboplatin and cisplatin [ ], and 5-FU. All combinations had additive or better than additive activity when compared to each agent alone."

Your presentation clearly suggests that Eloxatin is effective for the treatment of colon cancer and other solid tumors.

DDMAC requests that Sanofi immediately suspend all promotional activities and the dissemination of all promotional material for Eloxatin. Please address your response to the undersigned at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm 17-B-20, 5600 Fishers Lane, Rockville, Maryland 20857. Within ten business days of receiving this correspondence, please provide written notice of your intention to comply with this request. Your response should include a list of all materials that you have discontinued and the date of discontinuation. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 9076.

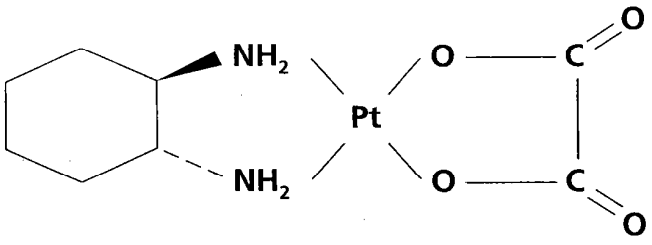
Sincerely,

/S/

Jean-Ah Choi, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

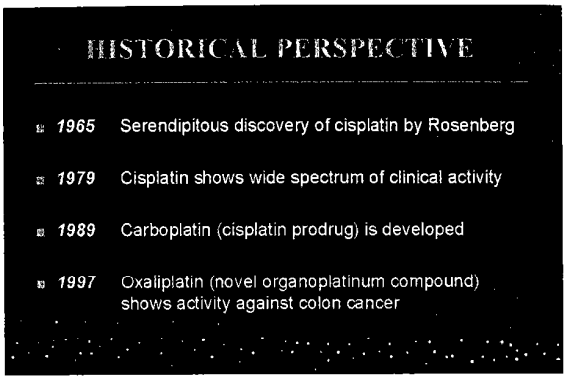
Oxaliplatin

A novel compound under investigation for the treatment of solid tumors



An overview of key characteristics, mechanism of action, pharmacodynam and pharmacokinetics

CONTENTS



Slide 1: HISTORICAL PERSPECTIVE

- The investigation of platinum (pt)-complexed compounds as antitumor agents in the 1960s led to the successful development of cisplatin (1). Cisplatin is currently used in the treatment of a variety of tumors, including testicular, ovarian, bladder, and lung. However, there are some significant toxicities associated with cisplatin therapy including severe nephrotoxicity, nausea, vomiting, ototoxicity, and myelosuppression.
- Additional Pt compounds of different chemical classes were designated as possible second-generation agents. To date, the only other platinum analogue that has been approved for clinical use as an antitumor agent is carboplatin. Carboplatin is basically a less potent prodrug of cisplatin and has a side-effect profile principally characterized by adverse hematological events. Over the years, various antitumor platinum complexes have been synthesized with the intention of both improving the antitumor activity and reducing the toxicity.
- The synthesis and initial characterization of 1,2-diaminocyclohexane platinum (DACH-Pt) complexes were first reported by several laboratories in the early 1970s as analogues or alternatives to cisplatin (2). Interest in DACH-Pt compounds was stimulated by the reports of Burchenal and coworkers (3, 4) that platinum complexes with the DACH carrier ligand were much more effective against cisplatin-resistant mouse L1210 leukemia cells, than platinum complexes with a variety of other carrier ligands.

Slide 1: HISTORICAL PERSPECTIVE, cont'd

- Subsequent studies showed that DACH-Pt compounds were effective against a variety of cisplatin-sensitive and cisplatin-resistant cell lines of both murine and human origin; however, DACH-Pt complexes were clearly not effective against all cisplatin-resistant cell lines.

1. Rosenberg BL, Van Camp JE, Trosko JE, Mansour VH. Platinum compounds: a new class of potent antitumour agents. Nature 1969;222:385-386.
2. Connors TA, Jones M, Ross WCJ, Braddock PD, Khokhar AR, Tobe ML. New platinum complexes with antitumour activity. Chem Biol Interact 1972;5:415-424.
3. Burchenal JH, Kalaher K, Dew K, Lokys L. Rationale for development of platinum analogs. Cancer Treat Rep 1979;63:1493-1498.
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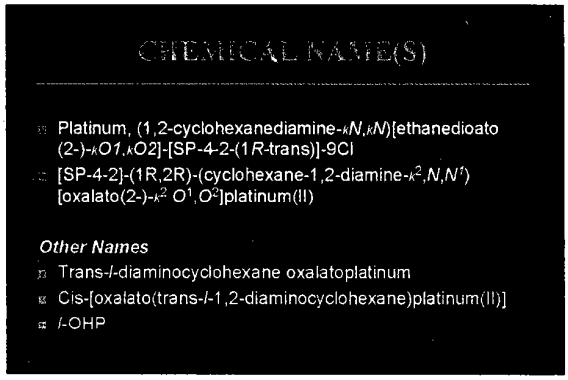
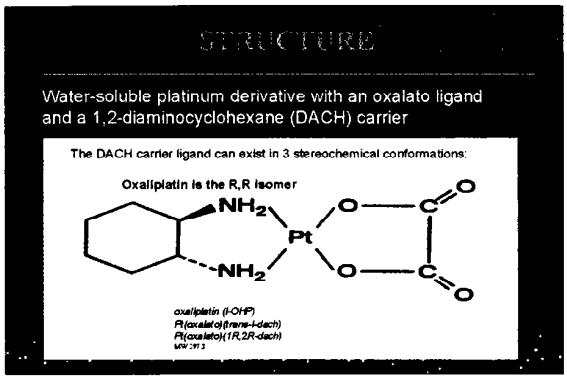


Slide 2: CHEMICAL NAME(S)



Slide 3: STRUCTURE

- Oxaliplatin (trans-*l*-diaminocyclohexane oxalatoplatinum) is a water-soluble platinum-complexed compound with an oxalate as the hydrolysable ligand and a diaminocyclohexane (DACH) as a carrier ligand.
- The synthesis and characterization of the DACH platinum compound was first reported by Burchenal et al (1) in the 1970s. The DACH carrier ligand can exist in 3 stereochemical conformations, of which the trans-1 (R, R) isomer was selected for clinical development because it was found to be more active in murine tumor models (2, 3).
- Among the known platinum derivatives, compounds bearing the DACH carrier ligand were shown to have antitumor activity in some cell lines with acquired resistance to cisplatin.
- Molecular weight: 397.3

1. Burchenal JH, Kalaher K, Dew K, Lokys L. Rationale for development of platinum analogs. Cancer Treat Rep 1979;63:1493-1498.
2. Kidani Y, Noji M, Tashiro T. Antitumor activity of platinum(II) complexes of 1,2-diaminocyclohexane isomers. Gann 1980;71:637-643.
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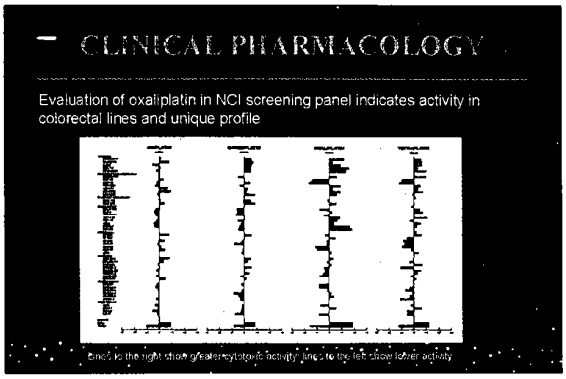
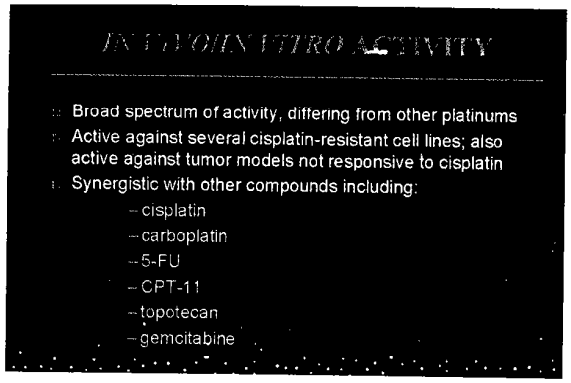


Slide 4: CLINICAL PHARMACOLOGY

This slide compares the antitumor activity of oxaliplatin with cisplatin in the NCI screening panel, which contains 47 cell lines, including cisplatin-resistant cell lines, derived from 8 different tissue types. Clearly, oxaliplatin has a different spectrum of activity and low cross-resistance to cisplatin (1).

1. Rixe O, Ortuzar V, Alvarez M, et al. Oxaliplatin, tetraplatin, cisplatin and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol 1996;52:1855-1865.



Slide 5: IN VIVO/IN VITRO *ACTIVITY*

Oxaliplatin demonstrates a broad spectrum of *in vitro* cytotoxic and *in vivo* antitumor activity that differs from that of either cisplatin or carboplatin. In addition, oxaliplatin is active against several cisplatin-resistant cell lines, colon carcinoma, and other solid tumors that are not responsive to cisplatin. Also, oxaliplatin in combination with 5-fluororacil (5-FU) leads to synergistic antiproliferative activity *in vitro* as well as *in vivo* synergism in several tumor models.

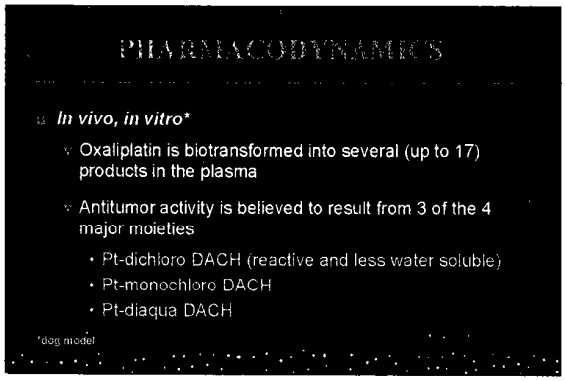
In vitro tumor cell cytotoxicity studies have been conducted with oxaliplatin in combination with SN-38 (the active metabolite of CPT-11) (1), tirapazamine (a hypoxic cytotoxic agent), cisplatin (2), and 5-FU. In all cases, the results indicated that the combination exposures were additive or greater than additive in the various cell lines tested.

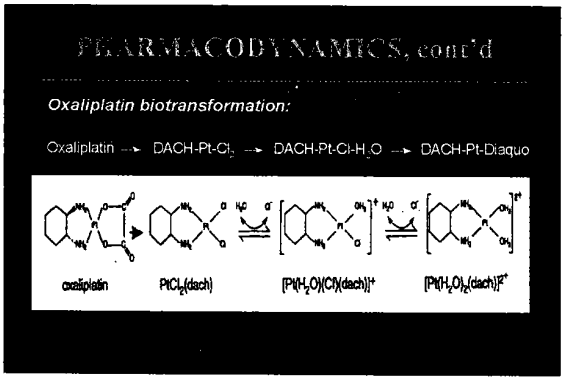
The studies with 5-FU plus oxaliplatin in colon cell lines are of particular interest, since this led to the proposed clinical use. Oxaliplatin in combination with 5-FU produced synergistic cytotoxicity in the following cell lines: HT-29 colon; a 5-FU-resistant colon cell line; HT-29FU; CaCo2 colon; MDA-MD231 breast; and 2008 ovarian. These results support the clinical indication of 5-FU plus oxaliplatin in the treatment of colon carcinoma.

In vivo antitumor studies were conducted with oxaliplatin in combination with CPT-11, cyclophosphamide (3), mitomycin-C, carboplatin and cisplatin (4, 5), and 5-FU. All combinations had additive or better than additive activity when compared to each agent alone.

Slide 5: IN VIVO/IN VITRO *ACTIVITY, cont'd*

1. Zeghari-Squalli N, Misset JL, Cvitkovic E, et al. Mechanisim of the in vitro synergism between SN38 and oxaliplatin (abstract). Proc Amer Assoc Cancer Res 1997;38:3.
2. Rixe O, Ortuzar W, Alvarez M, et al. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institue's Anticancer Drug Screen Panel. Biochem Pharmacol 1996;52:1855-1865.
3. Gale GR, Atkins LM, Meischen SJ, Schwartz P. Synergistic action of high-dose hydroxyurea when used with cyclophosphamide and certain new organoplatinum complexes in treatment of advanced L1210 leukemia. Cancer 1978;41:1230-1234.
4. Mathé G, Chenu E, Bourut C. Experimental study of three platinum complexes: CDDP, CBDCA and L-OHP on L1210 leukemia: alternate or simultaneous association of two platinum complexes (abstract). Invest New Drugs 1989;7:404.
5. Mathé G, Kidani Y, Segiguchi M, et al. Oxalato-platinum or L-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.
6. Ortuzar W, Paull K, Rixe O, et al. Comparison of the activity of cisplatin (CP) and oxaliplatin (OXALI) alone or in combination in parental and drug resistant sublines. Proc Am Assoc Can Res 1994;35:332.
7. Raymond E, Buquet-Fagot, Djelloul, et al. Antitumor activity of oxaliplatin in combination with 5 Fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. Anticancer Drugs 1997;8:876-885.
8. Zeghari-Squalli N, Misset JL, Goldwasser F, et al. Cellular pharmacology of SN38 in combination with oxaliplatin or with oxaliplatin in human colon cancer cells. Proc Am Soc Clin Oncol 1997;16:255a.





Slides 6 and 7: PHARMACODYNAMICS

In vitro antitumor activity

The pharmacodynamic effects of oxaliplatin were investigated in multiple *in vitro* and *in vivo* studies. Oxaliplatin, like other platinum (Pt)-related complexes, readily undergoes nonenzymatic reactions known as biotransformations (1). Oxaliplatin can be converted *in vitro* and *in vivo* to the more reactive and less water-soluble Pt-dichloro DACH, as well as the monochloro DACH and diaqua DACH moieties. As a result, the antitumor activity of oxaliplatin described below is likely due to biotransformed products of oxaliplatin.

Oxaliplatin has a broad spectrum of *in vitro* antiproliferative activity against a variety of murine and human tumor cell lines.

Slides 6 and 7: PHARMACODYNAMICS, cont'd

In vivo antitumor activity

Oxaliplatin has shown equal or superior *in vivo* antitumor activity when compared to cisplatin in a variety of murine tumor models.

1. Chaney SG. The chemistry and biology of platinum complexes with the1,2-diamino-cyclohexane carrier ligand (Review). Int J Oncol 1995;6:1291-1305.
2. Silvestro L, Anal H, Sommer R, Trincal G, Tapiero H. Comparative effects of a new platinum analog (trans-l-diaminecyclohexane oxalatoplatinum; L-OHP) with CDDP on various cells: correlation with intracellular accumulation. Anticancer Res 1990;10:1376.
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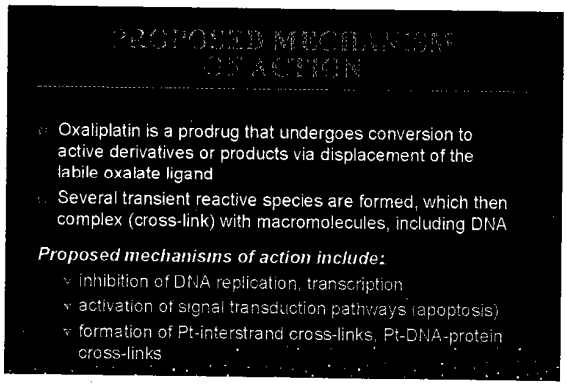
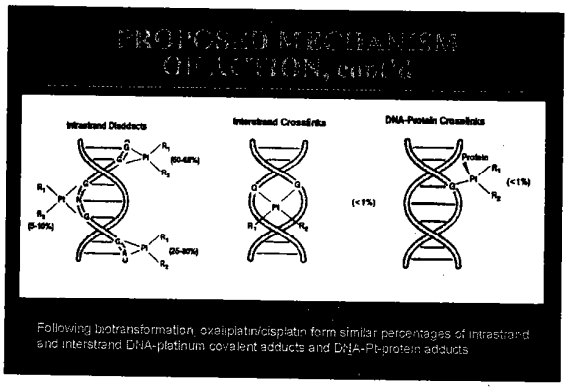
6. Pendyala L, Creaven PJ, Perez R, Zdanowicz JR, Raghavan D. Intracellular glutathione and cytotoxicity of platinum complexes. Cancer Chemother Pharmacol 1995;36:271-278.
7. Fukuda M, Ohe Y, Kanzawa F, et al. Evaluation of novel platinum complexes, inhibitors of topoisomerase I and II in non-small cell lung cancer (NSCLC) sublines resistant to cisplatin. Anticancer Res 1995;15:393-398.
8. Rietbroek RC, van de Vaart PJM, Haveman J, Blommaert FA, Geerdink A, Bakker PJM, Veenhof CHN. Hyperthermia enhances the cytotoxicity and platinum-DNA adduct formation of lobaplatin and oxaliplatin in cultured SW 1573 cells. J Cancer Res Clin Oncol 1997;123:6-12.
9. Riccardi A, Meco D, Lasorella A, et al. Comparison of cytotoxity of oxaliplatin, cisplatin and carboplatin in human neuroblastoma (NB) cell lines (abstract). Proc Am Soc Clin Oncol 1997;16:249a.
10. Dunn TA, Schmoll HJ, Grunwald V, Bokemeyer C, Casper J. Comparative cytotoxicity of oxaliplatin and cisplatin in non-seminomatous germ cell cancer lines. Invest New Drug 1997;15:109-114.
11. McSherry P. In vitro stability of [3H]-Oxaliplatin in dog blood, plasma and ultrafiltrate and urine. Sanofi, internal report 30 July 1997.





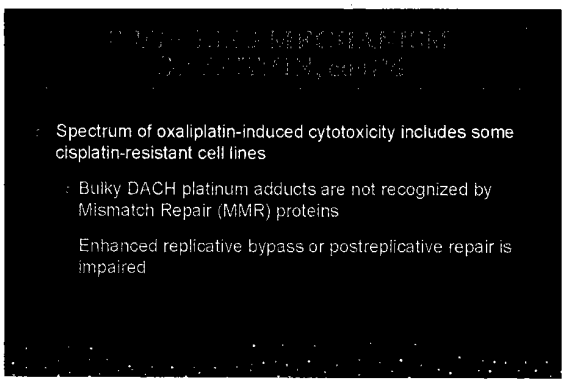
Slides 8 and 9: PROPOSED MECHANISM OF ACTION

Antitumor activities associated with platin compounds, including oxaliplatin

Studies conducted to date indicate that the mechanism of action of oxaliplatin is similar to that of other platins in terms of types and percentages of DNA-Pt adducts formed (1, 2). Oxaliplatin forms inter- and intrastrand DNA-Pt adducts/cross-links between 2 adjacent or close guanines (GG or GNG) or adjacent guanine-adenine (GA) base pairs. The formation of these DNA-Pt cross-links inhibits DNA replication and transcription, resulting in cell death in actively dividing cells. In addition, oxaliplatin, as well as other Pt compounds, can result in DNA-protein cross-links, although to a lesser extent.

Slides 8 and 9: PROPOSED MECHANISM OF ACTION, cont'd

1. Saris CP, van de Vaart PJM, Rietbroek RC, et al. In vitro formation of DNA adducts by cispl lobaplatin and oxaliplatin in calf thymus DNA in solution and in cultured human Carcinogenesis 1996;17:2763-2769; also abstract 280:9th NCI-EORTC symposium 1996:82.
2. Butour JL, Mazard AM, Macquet JP. Kinetics of the reaction of cis-platinum compounds with in vitro. Biochem Biophysical Res Commun 1985;133:347-353.



Slide 10: PROPOSED MECHANISM OF ACTION, CONTINUED

Possible mechanism of platinum resistance

Currently, there is limited information on the possible mechanisms of tumor cell resistance to oxaliplatin. To date, the only resistance mechanisms that have reproducibly been shown to discriminate between cisplatin and DACH-Pt compounds such as oxaliplatin, are defects in mismatch repair and enhanced replicative bypass (postreplicative repair).

Human colon carcinoma cell lines deficient in mismatch repair enzymes were 2-fold resistant to cisplatin, but had little or no resistance to oxaliplatin. Also, defects in mismatch repair of human colon carcinoma cells produced cisplatin resistance, but not oxaliplatin resistance, in an *in vivo* xenograft model (1, 2, 3).

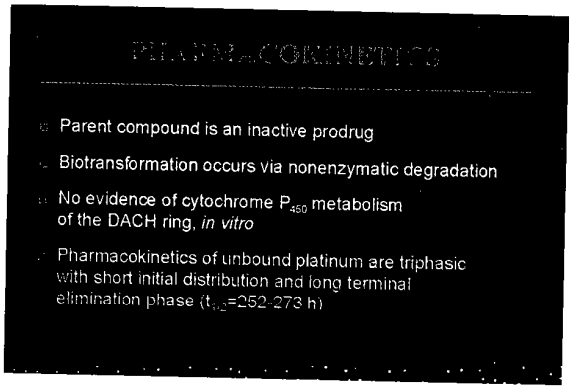
Unique properties associated with the mechanism of action of oxaliplatin

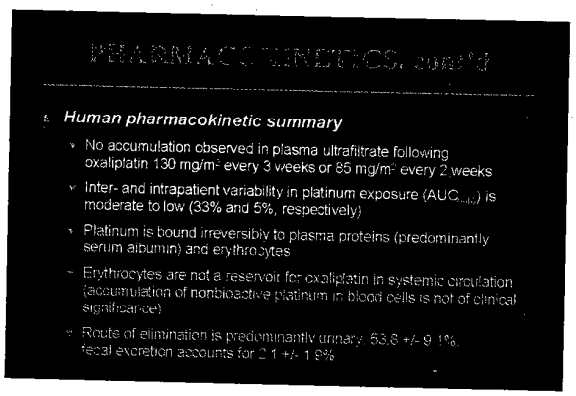
Preclinical data suggest several unique attributes related to the cytotoxic/antitumoral activity of oxaliplatin:

- DACH-Pt adducts are bulkier and more hydrophobic than cis-diamine-Pt adducts and may be more effective in DNA synthesis inhibition (4, 5).
- DNA mismatch repair complexes do not recognize DACH-Pt adducts (1, 2, 3).

Slide 10: PROPOSED MECHANISM OF ACTION, CONTINUED, cont'd

1. Fink D, Nebel S, Aebi S, et al. The role of DNA mismatch repair in platinum drug resistance. Cancer Res 1996;56:4881-4886.
2. Aebi S, Kurdi-Haidar B, Gordon R, et al. Loss of DNA mismatch repair in acquired resistance to cisplatin. Cancer Res 1996;56:3087-3090.
3. Fink D, Zheng H, Nebel S, et al. In vitro and in vivo resistance to cisplatin in cells that have lost DNA mismatch repair. Cancer Res 1997;57:1841-1845.
4. Boudny V, Vrana O, Gaucheron F, Kleinwachter V, Leng M, Brabec V. Biophysical analysis of DNA modified by 1,2-diaminocyclohexane platinum(II) complexes. Nucleic Acids Res 1992;20:267-272.
5. Mamenta EL, Poma EE, Kaufmann WK, Delmastro DA, Grady HL, Chaney SG. Enhanced replicative bypass of platinum-DNA adducts in cisplatin-resistant human ovarian carcinoma cell lines. Cancer Res 1994;54:3500-3505.





Slides 11 and 12: PHARMACOKINETICS

The pharmacokinetics of platinum in plasma, plasma ultrafiltrate, and blood cells has been investigated following a 2-hour oxaliplatin infusion of 130 mg/m², every 3 weeks for 1 to 5 cycles. The pharmacokinetics of platinum in plasma ultrafiltrate were characterized by a 3-compartment open model with initial α and β distribution phases of 0.28 ± 0.06 h and 16.3 ± 2.90 h, respectively, and a γ-elimination phase of 273 ± 19.0 h.

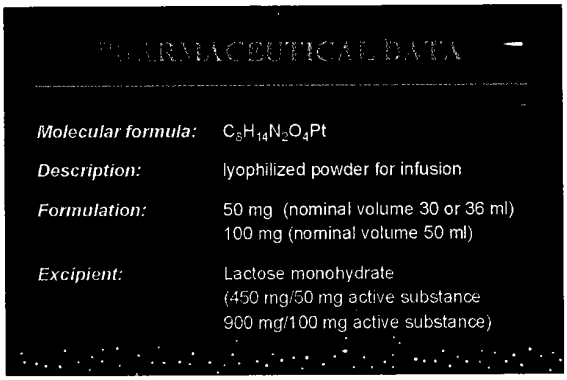
Biotransformation *in vitro* is considered to be the result of nonenzymatic degradation, and there is no evidence of cytochrome P_{450}-mediated metabolism of the diaminocyclohexane (DACH) ring. Oxaliplatin undergoes extensive biotransformation and is undetectable in plasma

Slides 11 and 12: PHARMACOKINETICS, cont'd

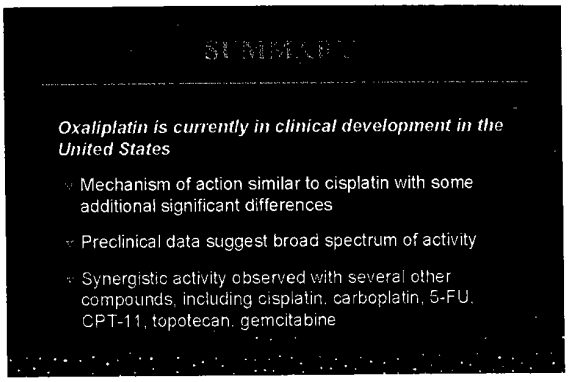
ultrafiltrate at the end of a 2-hour infusion at 130 mg/m². At least 10 biotransformation products are present in plasma.

The majority of platinum is eliminated in the urine, primarily within the first 0-48 hours. By day 5, approximately 54% of the total dose was recovered in the urine and <3% in the feces. A significant decrease in the clearance of ultrafiltrable platinum from 17.5 ± 8.17 L/hr, to 9.95 ± 5.73 L/hr was observed in moderate renal impairment; however, this was not associated with an increased incidence of toxicity.

1. Extra JM, Marty M, Brienza S, Misset JL. Pharmacokinetics and safety profile of oxaliplatin. Sem Oncol 1998;25:13-22.



Slide 13: PHARMACEUTICAL DATA



Slide 14: SUMMARY

Physical properties

- White to off-white crystalline powder
- Slightly soluble in water (solubility in water at 20°C is 6 mg/ml)
- Very slightly soluble in methanol (solubility in methanol at 20°C is 0.125 mg/ml)
- Practically insoluble in ethanol and acetone
- The pH of an aqueous solution of 2 mg/ml is between 4.8 and 5.7.

Reconstitution

The freeze-dried powder is reconstituted by adding 10 to 20 ml (for the 50-mg vials) or 20 to 40 ml (for the 100-mg vials) of water for injection or 5% glucose solution and then diluting in an infusion solution of 250 ml or 500 ml of 5% glucose solution.

Stability

The freeze-dried powder is stable for 3 years at room temperature. The reconstitution (eg, 10 to 40 ml of water for injection or 5% glucose solution) can be stored in the original vial for up to 48 hours at 2°C to 8°C; the final dilution for IV infusion (ie, 250 to 500 ml of 5% glucose solution) is stable for 24 hours at room temperature.

Incompatibility

Reconstitution must never be performed using a sodium chloride solution. Other incompatibilities are the following: alkaline drugs or media, such as basic solutions of 5-FU, trometamol, needles, or IV infusion sets containing aluminum components.

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Butour JL, Mazard AM, Macquet JP. Kinetics of the reaction of cis-platinum compounds with DNA in vitro. Biochem Biophysical Res Commun 1985;133:347-353.

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Dunn TA, Schmoll HJ, Grunwald V, Bokemeyer C, Casper J. Comparative cytotoxicity of oxaliplatin and cisplatin in non-seminomatous germ cell cancer lines. Invest New Drug 1997;15:109-114.

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