

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-492 SE8- s008

Drug name: ELOXATIN®

Generic name: Oxaliplatin

Formulation: 50 mg or 100 mg vial of sterile, preservative-free lyophilized powder for reconstitution

Adult Indication: Metastatic carcinoma of the colon or rectum

Pediatric Indication: None

Current Submission: Pediatric Supplement

Applicant: Sanofi-Aventis US Inc.
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807

OCP Division: Division of Clinical Pharmacology 5 (HFD-860)

OODP Division: Division of Drug Oncology Products (HFD-150)

Submission Dates: 10-July-2006

Primary Reviewer: Roshni Ramchandani, Ph.D.

**Pharmacometrics
Team Leader:** Joga Gobburu, Ph.D.

Team Leader: Brian Booth, Ph.D.

Type of Submission: NDA-Supplement

(b) (4)

Information that is deleted, it is indicated by a strikethrough. New text is indicated in green text.

Agency's Proposed Labeling:

Under sections:

- FULL PRESCRIBING INFORMATION:CONTENTS
- 8. USE IN SPECIFIC POPULATIONS
- 8.4 Pediatric Use

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in (b) (4) 105 pediatric patients during the first cycle. The average clearance in pediatric patients estimated by the population pharmacokinetic analysis was (b) (4) 4.7 L/h/m². The inter-patient variability of platinum clearance in pediatric cancer patients was (b) (4) 1%.

Mean platinum pharmacokinetic parameters in ultrafiltrate were C_{max} of (b) (4) (b) (4) 0.75 ± 0.24 µg/mL, AUC₀₋₄₈ of (b) (4) 7.52 ± 5.07 µg.h/mL and AUC_{inf} of (b) (4) 8.83 ± 1.57 µg.h/mL at 85 mg/m² of oxaliplatin and C_{max} of (b) (4) 1.10 ± 4.28 µg/mL, AUC₀₋₄₈ of (b) (4) 9.74 ± 2.52 µg.h/mL and AUC_{inf} of (b) (4) 17.30 ± 5.34 µg.h/mL at 130 mg/m² of oxaliplatin.

(b) (4)

B. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The applicant has conducted two phase 1 studies to characterize the safety and pharmacokinetics (PK) of oxaliplatin in children with advanced solid tumors. Oxaliplatin was given as a single agent in a weekly regimen in one study and an every-3-week regimen in the other study.

The applicant has also conducted two phase 2 studies to characterize the safety, PK and activity of oxaliplatin in patients with advanced CNS tumors. Oxaliplatin was given at a dose of 130 mg/m² every 3 weeks in both studies.

The PK data from the four studies were combined and a population PK model was developed to describe the PK of oxaliplatin. A three-compartment model, with inter-individual variability on CL, V2 and V3 and with a proportional residual error model, described platinum concentrations in plasma ultrafiltrate (PUF) collected in pediatric cancer patients. Inter-individual variability of PUF platinum clearance was significantly related to body weight and glomerular filtration rate. The residual variability for the final model was 41%.

Oxaliplatin exposures seen in pediatric and adult patients were comparable both in plasma and PUF, following comparable doses of 130 mg/m². This suggests that the PK parameters for pediatric and adult patients are comparable. The population mean oxaliplatin clearance in pediatric patients is 5.1 L/hr or 4.7 L/hr/m² (%CV=41%) when normalized for body surface area (BSA). The estimate of oxaliplatin clearance in adults is reported to be 9.3 L/hr at 130 mg/m². Using a nominal BSA of 1.73 m², these clearances would translate to 5.4 L/hr/m². These estimates indicate that the PK in pediatric patients can be predicted from adults.

The sponsor also conducted an exposure-response analysis to examine the relationship between exposure and incidence of various toxicities associated with oxaliplatin, including neutropenia, thrombocytopenia, GI toxicities (nausea, vomiting, diarrhea) and CNS toxicities (peripheral neuropathy). An analysis conducted in patients with exposure (AUC) data did not reveal any significant association between incidence of severe (grade 3/4) toxicity and exposure across studies.

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/s/

Brian Booth
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