1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of this sNDA supplement N21492\S008 for Eloxatin® (oxaliplatin for injection) to add information from the pediatric cancer trials to the label.

1.2 Recommendation on Postmarketing Actions

No new recommendations. Continue post-marketing surveillance

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The oxaliplatin pediatric program consists of 4 studies – 2 Phase 1 studies (ARD5531 and DFI7434) and 2 Phase 2 studies (ARD5021 and ARD5530) involving 159 patients ages 7 months to 22 years with advanced and/or refractory solid tumors. Only 1 partial response was observed in the entire program (1/159, 0.25%).

In a Phase 1-2 study (ARD5531), oxaliplatin was administered as a 2-hour IV infusion on days 1, 8 and 15 every 4 weeks (1 cycle), for a maximum of 6 cycles, to 43 patients with refractory or relapsed malignant solid tumors, mainly neuroblastoma and osteosarcoma. Twenty eight (28) pediatric patients in the Phase I study received oxaliplatin at 6 dose levels starting at 40 mg/m² with escalation to 110 mg/m². The dose limiting toxicity (DLT) was sensory neuropathy at the 110mg/m² dose. Fifteen (15) patients received oxaliplatin at a dose of 90 mg/m² IV in the Phase II portion of the study. At this dose, paresthesia (60%, G3/4: 7%), fever (40%, G3/4: 7%) and thrombocytopenia (40%, G3/4: 27%) were the main adverse events. No responses were observed.

In a second Phase 1 study (DFI7434), oxaliplatin was administered to 26 pediatric patients as a 2-hour IV infusion on day 1 every 3 weeks (1 cycle) at 5 dose levels starting at 100 mg/m² with escalation to 160 mg/m², for a maximum of 6 cycles. In a separate cohort, oxaliplatin 85 mg/m² was administered on day 1 every 2 weeks, for a maximum of 9 doses. Patients had metastatic or unresectable solid tumors mainly neuroblastoma and ganglioneuroblastoma. The DLT was sensory neuropathy at the 160 mg/m² dose. Based on these studies, oxaliplatin 130 mg/m² as a 2-hour IV infusion on day 1 every 3

weeks (1 cycle) was used in subsequent Phase II studies. A dose of 85 mg/m^2 on day 1 every 2 weeks was also found to be tolerable. No responses were observed

In one Phase 2 study (ARD5021), 43 pediatric patients with recurrent or refractory embryonal CNS tumors received oxaliplatin 130 mg/m2 every 3 weeks for a maximum of 12 months in absence of progressive disease or unacceptable toxicity. In patients < 10 kg the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were leukopenia (67%, G3/4: 12%), anemia (65%, G3/4: 5%), thrombocytopenia (65%, G3/4: 26%), vomiting (65%, G3/4: 7%), neutropenia (58%, G3/4: 16%) and sensory neuropathy (40%, G3/4: 5%). One partial response was observed.

In a second Phase 2 study (ARD5530), 47 pediatric patients with recurrent solid tumors, including Ewing sarcoma or peripheral PNET, osteosarcoma, rhabdomyosarcoma and neuroblastoma, received oxaliplatin 130 mg/m2 every 3 weeks for a maximum of 12 months or 17 cycles. In patients $\leq$ 12 months old the oxaliplatin dose used was 4.3 mg/kg. The most common adverse events reported were sensory neuropathy (53%, G3/4: 15%), thrombocytopenia (40%, G3/4: 26%), anemia (40%, G3/4: 15%), vomiting (32%, G3/4: 0%), nausea (30%, G3/4: 2%) and AST increased (26%, G3/4: 4%). No responses were observed.

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 109 pediatric patients during the first cycle. The median clearance in pediatric patients estimated by the population pharmacokinetic analysis was 4.80 L/h. The inter-patient variability of platinum clearance in pediatric cancer patients was 40.9 %. Mean platinum pharmacokinetic parameters in ultrafiltrate were C_{max} of 754 $\pm$ 244 ng/mL, AUC_{0-48} of 7520 $\pm$ 5070 ng·h/mL and AUC of 8830 $\pm$ 1570 ng·h/mL at 85 mg/m² of oxaliplatin and C_{max} of 1100 $\pm$ 428 ng/mL, AUC_{0-48} of 9740 $\pm$ 2520 ng·h/mL and AUC of 17300 $\pm$ 5340 ng·h/mL at 130 mg/m² of oxaliplatin. PK parameters are similar to the ones observed in adults. No PK/PD was done due to low response rate in this population (< 1%)

Thus, oxaliplatin is ineffective in the regimens tested in children with refractory solid tumors, with an objective response rate of 1 out of 159 patients (0.25%)

1.3.2 Efficacy:

Only 1 reported partial response out of 159 patients was observed (< 1% of objective response rate). Thus, it appears that oxaliplatin is ineffective in the regimens tested in children with refractory solid tumors.

1.3.3 Safety:

In general, the safety profile of oxaliplatin in the pediatric population was similar to the one observed in the adult population. A total of 98 deaths were reported in all trials. Two of them occurred during the trial (1 case associated with dehydration and the other due to SVC syndrome) and 13 occurred within 28 days after last dose. All deaths were clearly or likely due to disease progression. This is expected in a population with very advanced and refractory metastatic solid tumors. Assessment of cause of AEs is difficult in this

end-stage population. SAEs occurred in ~ 20 % of patients. SAEs seen in 2 or more patients were: headache, hypersensitivity reactions, convulsions and sensory neuropathy. AEs leading to discontinuations were as follows: 3 cases of thrombocytopenia, 2 cases of hypersensitivity reactions and 1 each: pain, dehydration, bone pain, tumor pain, Horner's syndrome, urinary retention, pleural effusion, respiratory distress, hematoma and 1 SVC occlusion. Most common AEs were leukopenia, thrombocytopenia, anemia, vomiting and sensory neuropathy.

1.3.4 Dosing Regimen and Administration:

Based on study ARD5531, the recommended Phase 2 dose was 90 mg/m2 oxaliplatin administered IV over 2 hours. Sixteen patients were treated at this dose in this trial. However, in both Phase 2 trials ARD5021 and ARD5530, the dose was 130 mg/m2 oxaliplatin administered IV over 2 hours every 3 weeks. For patients < 10 kg, the dose was 4.3 mg/kg.

1.3.5 Drug-Drug Interactions

None reported in pediatric trials.

1.3.6 Special Populations

These studies were performed in kids, ages 7 months until 21 years of age.

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