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APPLICATION NUMBER:

211215Orig1s000

CLINICAL REVIEW(S)

Date: February 15, 2019
From: Rekha Kambhampati, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Deputy Director
Division of Cardiovascular and Renal Products
Subject: NDA 211215 Bivalirudin Injection, 5 mg/mL [50 mL vial] and presumed case of oliguric Acute Tubular Necrosis (ATN) requiring renal replacement therapy with extended IV lorazepam infusion containing Polyethylene glycol (PEG) 400

Background
Bivalirudin is a direct thrombin inhibitor approved for anticoagulation in certain patients undergoing percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI). MAIA has submitted a 505(b)(2) NDA for ANGIOMAX (bivalirudin) for Injection as a new ready-to-use formulation of bivalirudin injection dosed as a 0.75 mg/kg IV bolus immediately followed by a 1.75 mg/kg/hr IV infusion for the duration of the PTCA or PCI and up to four hours post-PCI in patients with ST-segment elevation MI. This new ready-to-use formulation utilizes polyethylene glycol (PEG) 400 as an excipient at a maximum dosage of 300 mg/kg/day.

Because PEG 400 has been associated with nephrotoxicity, the Agency requested that the applicant perform a literature review of the renal effects of PEG 400. The submitted literature review included ten non-clinical studies and a case report of ATN in a patient receiving an extended IV lorazepam infusion containing PEG 400. The applicant concluded that the preclinical studies did not suggest a renal-related safety concern with the dose of PEG 400 in the MAIA bivalirudin product, noting that most of the observed electrolyte abnormalities and/or nephrotoxic effects in the preclinical studies occurred at human equivalent dosages much higher than that found in the MAIA bivalirudin product (>1 g/kg/day). FDA's pharmacology-toxicology agreed with the applicant's conclusion. Biopharmaceutics has requested clinical input on the case report of ATN and whether the report raises concern about the renal safety of the dosage of PEG 400 in the MAIA bivalirudin product.

Materials Reviewed
A. Memo with consult question and brief summaries of product and case report
B. FDA CDER's Inactive Ingredients Database for Approved Drug Products
C. Response to information request entitled "Literature Review: Safety of Polyethylene Glycol (PEG 400) on the Kidney When Dosed by the Intravenous (IV) Route of Administration"
D. Case Report: Laine, GA, et al. Polyethylene Glycol Nephrotoxicity Secondary to Prolonged High-Dose Intravenous Lorazepam. *Ann Pharmacother*. 1995; 29: 1110-4.

Additional Background
PEG 400 is an excipient listed in FDA CDER's Inactive Ingredients Database for Approved Drug Products for intravenous administration with a recommended maximum concentration of 30%. PEG 400 has been associated with hemolysis at high concentrations and with nephrotoxicity at dosages >1

g/kg/day. Given that PEG 400 is renally cleared, the kidney is the organ that is thought to be exposed to the highest concentrations of PEG 400 in the body. IV lorazepam drip contains both PEG 400 and propylene glycol. Both of these excipients have very similar laboratory and renal toxicity profiles, namely, anion-gap metabolic acidosis, osmolar gap, lactic acidosis, and ATN. While the exact mechanism for renal injury is unclear, it is thought that the PEG 400 and propylene glycol create osmotic nephrosis resulting in swelling and vacuole formation of the renal tubular cells, eventually leading to renal injury. In addition, propylene glycol appears to disrupt renal tubular cell membrane integrity, further contributing to renal tubular injury[3].

Summary of Case Report by Laine, et al[1]

The patient was a 57-year-old, 82.7 kg man with a past medical history notable for chronic alcohol abuse who was admitted with acute respiratory distress secondary to probable community acquired pneumonia. His admission labs were notable for a creatinine of 71 µmol/L (0.8 mg/dL). Given inadequate treatment of his alcohol withdrawal, he was started on an IV lorazepam drip on day 2 of his hospitalization. His lorazepam drip dosage was in flux throughout his hospitalization with a maximum daily dosage of 228 mg (containing 11.5 gm of PEG 400) occurring on day 16. Initially, the patient's BUN and creatinine appeared to increase and decrease as the IV lorazepam drip dosage was increased and decreased, respectively. However, by hospital day 43, the patient's BUN and creatinine continued to rise despite discontinuation of the IV lorazepam drip the day prior. The patient cumulatively received 248 gm of PEG 400 over 45 days of his hospitalization. During his hospitalization, he was exposed to several other nephrotoxins, such as infection and various antibiotics, including vancomycin (**TABLE 1**). He was eventually diagnosed with acute tubular necrosis (ATN). On day 53, his renal function deteriorated further, requiring the initiation of renal replacement therapy (creatinine 477 µmol/L (5.4 mg/dL)). Eventually, the patient's renal function improved, and renal replacement therapy was discontinued on day 71 of his hospitalization. The patient achieved complete renal recovery prior to hospital discharge.

Laine, et al concluded that because other apparent causes of ATN, such as supra-therapeutic vancomycin levels or hemodynamic instability were ruled out, the patient's ATN resulted from "chronic exposure to moderate amounts of PEG-400 via the lorazepam injection[1]."

The applicant concluded that given that the patient's lorazepam infusion also contained propylene glycol, a known nephrotoxin, the etiology for the patient's nephrotoxicity (PEG 400 versus the propylene glycol) could not be determined with certainty.

[1]Laine, GA, et al. Polyethylene Glycol Nephrotoxicity Secondary to Prolonged High-Dose Intravenous Lorazepam. *Ann Pharmacother*. 1995; 29: 1110-4

[2]Tayar, J, et al. Severe hyperosmolar metabolic acidosis due to large dose of intravenous lorazepam [letter]. *N Engl J Med*. 2002; 346 (16): 1253-4

[3]Mullins, ME and BJ Barnes. Hyperosmolar Metabolic Acidosis and Intravenous Lorazepam [letter]. N Engl J Med. 2002; 347 (11): 857-8

[4]Yorgin, PD, et al. Propylene glycol-induced proximal renal tubular cell injury. *Am J Kidney Dis*. 1997; 30: 134-9

Table 1: Lorazepam/Polyethylene Glycol Dosage Versus Selected Laboratory Values and Drug Therapy

DAY	DAILY LORAZEPAM DOSE (mg)[a]	CUMULATIVE LORAZEPAM DOSE (mg)	DAILY PEG DOSE (mL)[a]	CUMULATIVE PEG DOSE (mL)	PROTEIN INTAKE (g/kg/d)	BUN (mmol/L)	SCr (μmol/L)	AST (U/L)	BILIRUBIN (μmol/L)	OTHER POTENTIAL NEPHROTOXINS
1	14	14	1.3	1.3	0	3.9	71	82	13.7	
4	96	302	3.6	14.2	1.0	3.9	62			
8	96	686	4.3	31.4	1.0	5.7	62			CIP/VANC (day 10)[b]
12	204	1502	9.2	68.0	1.0	10.7	80			
16	228	2414	10.2	109.0	1.0	12.1	62	47	8.6	
20	206	3238	9.3	146.2	1.0	15.3	80			CIP/VANC D/C (day 23)
24	17	3306	0.9	149.8	1.0	9.3	80	74	5.1	CEFTAZ (day 24)[c]
28	31	3430	2.8	161.0	1.5	6.4	62			
32	69	3706	6.2	185.8	1.5	7.5	62			VANC (day 31)[d]
34	70	3846	6.3	198.4	1.5	14	53	85	3.4	CEFTAZ D/C (day 33)
36	48	3942	4.3	207.0	1.5	22	80			VANC D/C (day 35)
38	36	4014	3.2	213.4	1.5	19	71			
40	18	4050	1.6	216.6	1.5	15	80			
42	12	4074	1.1	218.8	1.5	18	71			
43	8	4082	0.7	219.5	1.5	26	124	71	6.8	
44	3	4085	0.3	219.8	1.5	42	274			
45	4	4089	0.4	220.2	1.5	47	327			

AST = aspartate aminotransferase; BUN = blood urea nitrogen; CEFTAZ = ceftazidime; CIP = ciprofloxacin; D/C = discontinued; PEG = polyethylene glycol-400; SCr = serum creatinine; VANC = vancomycin.
[a]Average daily dose administered between the time periods indicated in the first column.
[b]Ciprofloxacin 750 mg NG q12h and vancomycin 1 g iv q12h.
[c]Ceftazidime 2 g iv q8h.
[d]Vancomycin 1 g iv q12h.

Another Relevant Case[2]

Tayar, et al described a case of severe hyperosmolar metabolic acidosis and renal failure requiring temporary renal replacement therapy in a 34-year-old woman with alcohol abuse who was admitted for acute respiratory distress secondary to sepsis from *Escherichia coli* pneumonia whose alcohol withdrawal was treated with increasing doses of IV lorazepam drip (up to 30 mg/hr) (cumulative lorazepam dose of 1696 mg)[2,3]. Renal recovery was achieved after discontinuation of the lorazepam drip and initiation of temporary renal replacement therapy. Given the exposure to large amounts of PEG 400 in the lorazepam drip (cumulative dose 173 gm) and rapidly increasing osmolar gap, the authors concluded that the metabolic and renal abnormalities observed in their patient were secondary to the PEG 400 in the lorazepam gtt[2,3]. However, in a letter to the editor regarding the case described by Tayar, et al, Mullins and Barnes demonstrated that the propylene glycol (cumulative dose 704 gm) would have also had a considerable role in contributing to the hyperosmolar metabolic acidosis described and likely contributed to the observed renal failure as well[3].

[1]Laine, GA, et al. Polyethylene Glycol Nephrotoxicity Secondary to Prolonged High-Dose Intravenous Lorazepam. *Ann Pharmacother*. 1995; 29: 1110-4
[2]Tayar, J, et al. Severe hyperosmolar metabolic acidosis due to large dose of intravenous lorazepam [letter]. *N Engl J Med*. 2002; 346 (16): 1253-4
[3]Mullins, ME and BJ Barnes. Hyperosmolar Metabolic Acidosis and Intravenous Lorazepam [letter]. N Engl J Med. 2002; 347 (11): 857-8
[4]Yorgin, PD, et al. Propylene glycol-induced proximal renal tubular cell injury. *Am J Kidney Dis*. 1997; 30: 134-9

Question: Specifically, I would like to receive the MO's input regarding the attached literature clinical case report (Laine et al. 1995) provided as part of the Applicant's response to the IR. The Applicant indicated in the Literature Survey that 220 mL of PEG 400 was received (as high dose lorazepam IV injection) in that case over 43 days (PEG 400 MDD range: 0.04 – 0.123 mL/kg/day).

Response:
The patient was exposed to several agents that could result in ATN, namely, infection, vancomycin, PEG 400 (via lorazepam drip), and propylene glycol (via lorazepam drip). Based on the vancomycin peak (29 µg/mL) and trough levels (13 µg/mL), it seems less likely that the patient's ATN was secondary to vancomycin toxicity. However, it is difficult to conclude more than this. The patient's ATN could have been caused by infection, PEG 400, the propylene glycol, or a combination of these factors. Regardless, the cumulative dosage and duration of PEG 400 exposure in this case are far greater than the expected exposure to PEG 400 in the bivalirudin injection. In addition, the amount of PEG 400 in the bivalirudin injection (300 mg/kg/day) is much lower than the human equivalent dosages that were deemed toxic (>1 gm/kg/day) in non-clinical studies. In summary, the case does not raise concern for the renal-safety of the dosage of PEG 400 in the MAIA bivalirudin product.

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/s/

REKHA KAMBHAMPATI
02/15/2019 11:53:32 AM

ALIZA M THOMPSON
02/15/2019 12:04:02 PM