CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210864Orig1s000

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA	210864
SD#	29
Sequence Number	029
Sponsor	Sedor Pharmaceuticals, LLC
Drug	Sesquient (fosphenytoin sodium and betadex sulfobutyl ether sodium)
Proposed Indication	Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery. Short term substitution for oral phenytoin
Material Submitted	Class 2 NDA Resubmission
Correspondence Date	5/8/2020
Date Received	5/8/2020
Date Review Completed	10/22/20
Reviewer	Steven Dinsmore, DO

1. Background

This is a Class 2 resubmission NDA 210864 following a Complete Response on March 22, 2019 due to product quality and clinical safety issues.

The proposed indications for Captisol enabled fosphenytoin (CAP-fos), (Sesquient) are identical to those of the fosphenytoin sodium injection Listed Drug (LD) CEREBYX® (Cerebyx) on the basis of two Phase I clinical studies (A98 and 247) that demonstrated pharmacokinetic bioequivalence (BE) to Cerebyx for both intravenous (IV) and intramuscular (IM) administration. No new clinical efficacy study is necessary to bridge the CAP-fos API to the established indications of the LD. The new formulation of CAP-fos (Captisol-enabled fosphenytoin) is a drug comprised of fosphenytoin (USP) and includes betadex sulfobutyl ether sodium (Captisol®), (b) (4) room-temperature storage of the drug product at a more physiologic pH of 7(D)(4)–8.2. All other fosphenytoin injection products have a pH specification of 8.3-9.0. Room temperature storage allows improved availability in out-of-hospital emergency situations while the lower pH is more physiologic. Treatment with each milligram of phenytoin equivalents (PE) will be associated with 2 milligrams of Captisol. In addition to the demonstration of bioequivalence to the LD Cerebyx, this fosphenytoin formulation requires support for the safety of Captisol in the adult and pediatric populations for rate of Captisol infusion and total exposure to Captisol and for the safety of intramuscular administration; the limited safety data only supports some of the indications of the LD and does not support intramuscular administration, as discussed in Section 2, a, b and c of this review.

This New Drug Application (NDA) for Captisol-Fosphenytoin relies on the 505(b)(2) regulatory pathway. This is a 3rd cycle submission. The initial NDA was submitted on 5/22/2018 with a CR on 3/22/19 due to a product quality issue and lack of adequate information to support the safety of the Captisol excipient. There was a class 2 resubmission on 6/28/19 with a complete response on 12/20/2019 with deficiencies that included product quality issue due to foreign particles and regulatory deficiencies. These regulatory deficiencies included a required update of FDA form 356S to reflect reliance on only Cerebyx and

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Carnexiv NDAs, documentation of notice of Paragraph IV certification notice to Ligand Pharmaceuticals, owner of Cydex (a Ligand Company) that is the owner of Captisol and the Cydex DMF 14364. In addition, clear documentation of a receipt of Paragraph IV certification that was transmitted to Lundbeck Pharmaceuticals was needed.

In this, 3rd cycle, Class 2 resubmission the applicant has remedied the regulatory deficiencies and has verified reliance on Carnexiv for support of IV Captisol safety in adult patients. In the pediatric population, age 2 years or greater, there is support only for IV non-urgent loading of CAP-fos and maintenance dosing derived from the medical literature presented in DMF 14364. There is inadequate support for the allowance of IM dosing that is present in LD labeling.

2. Resubmission May 8, 2020 (cycle 3)

Clinical

There is no new clinical study data for review in this resubmission. In the original submission, safety data from two bioequivalence studies were examined and did not reveal a differential safety signal identified between test (CAP-fos) and reference (fosphenytoin) product in the bioequivalence studies, see NDA 210864 initial submission, clinical review. The clinical section of this review is directed at assessment of the support for the excipient Captisol that has been provided by the applicant.

a. CAP-fos IV Dosing and Support for Safety in Adult Patients

The Captisol associated fosphenytoin product is supplied in single dose vials containing 100mgPE/2ml while each milliliter of product contains 100mg Captisol. Thus, each 1mg of fosphenytoin is delivered with 2mg of Captisol. The labeled rate of delivery for status epilepticus (SE) in adults is up to 150mgPE/min of fosphenytoin. Rapid fosphenytoin infusion is also required for appropriate treatment of seizures occurring during neurosurgery. This results in Captisol delivery of 300mg/min during rapid loading. The total dose is up to 20mgPE/kg. This results in a total Captisol dose of 2800mg during a loading dose of a 70kg patient. A second, maintenance dose of fosphenytoin or phenytoin is recommended in the LD labeling at the next identified dosing interval. This maintenance dose is 3mgPE/kg. If on day 1 a maximum loading (20mgPK/kg) and maintenance dose (3mgPD/kg) are administered to a 70kg patient, this would result in a total day 1 dose of 1610 mg CAP-fos and an associated dose of 3220mg of Captisol. The applicant is reliant on right of reference to Carnexiv to support safety of Captisol at these doses; Carnexiv is only approved for adults. Carnexiv labeling supports, in adults, the maximum rate of Captisol infusion, the total day 1 loading, and the exposure associated with short term CAP-fos maintenance dosing as covered in the 2nd cycle Clinical Review of CAP-fos on page 3 in the section title “Reference to Carnexiv”.

b. CAP-fos IV Dosing and Support for Safety in Pediatric Patients

The LD labeled pediatric loading dose for SE is up to 20mgPE/kg at a maximum rate of 2mgPE/min. For CAP-fos, the associated Captisol delivery rate and total dose on day 1 of loading are shown by age and weight in Table 1. Maintenance dosing of CAP-fos in pediatric patients has a maximum of 6mgPE/kg/day in divided doses. After administration of a loading dose, maintenance doses should be started at the

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next identified dosing interval. This maintenance dose adds an additional maximum of 3mgPE/kg for Day 1 (6mgPE / 2), loading and maintenance dosing total. This total is shown in the final left column of Table 1.

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Table 1 CAP-fos Associated Captisol Infusion Rate by Age and Weight for Treatment of Status Epilepticus

age	weight in kg at 50th percentile for boys	CAP-fos delivered during loading dose	Maximum infusion rate of Captisol content during CAP-fos loading dose (2mg/kg/min)- Adult (150mg/min= 300mg Captisol / min)	Captisol Exposure associated with CAP-fos Loading dose	Maintenance Dose Day 1 CAP-fos dose @ 4mgPE/kg; Adult @ 6mgPE/kg	Maintenance Dose Day 1 CAP-fos, Captisol Exposure @ 4mgPE/kg CAP-fos: Adult @ 6mgPE/kg	Total Day 1 Captisol Exposure
2	12	240	48	480	48	96	576
3	15	300	60	600	60	120	720
4	16	320	64	640	64	128	768
5	18	360	72	720	72	144	864
6	21	420	84	840	84	168	1008
7	23	460	92	920	92	184	1104
8	26	520	104	1040	104	208	1248
9	28	560	112	1120	112	224	1344
10	32	640	128	1280	128	256	1536
11	36	720	144	1440	144	288	1728
12	40	800	160	1600	160	320	1920
13	46	920	184	1840	184	368	2208
14	50	1000	200	2000	200	400	2400
15	56	1120	224	2240	224	448	2688
16	61	1220	244	2440	244	488	2928
Adult	70	1400	300	2800	420	840	3640

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In this submission the applicant's referenced Captisol DMF 14364 is again reviewed for pediatric support of the Captisol infusion rate and exposure. This examination does not reveal adequate support for the rapid Captisol infusion required for treatment of SE or for seizures occurring during neurosurgery. However, there are 3 references identified that provide support for loading CAP-fos at a reduced rate and for the total Captisol exposure associated with a non-urgent loading dose and short-term substitution of oral phenytoin with CAP-fos. These references are 3 PK, safety and tolerability studies of intravenous voriconazole in the treatment of immunocompromised pediatric patients at risk for invasive fungal infections, see Table 2.

Intravenous voriconazole is solubilized for intravenous formulation with 16mg of Captisol for each mg of voriconazole. In all 3 references, the maximum voriconazole delivery rate is 3mg/kg/hr. This rate only yields Captisol infusion rates that are less than those achieved during CAP-fos, maximum infusion rates for pediatric patients during treatment of SE or seizures associated with neurosurgery, as shown in Table 4. The Captisol infusion rate associated with maximum CAP-fos infusion by weight is seen in the shaded column titled "CAP-fos" rate while the Captisol infusion rate associated with the maximum voriconazole infusion rate is seen in the column titled "voriconazole rate". The maximum Captisol infusion rate derived from the PK, Safety and Tolerability references (3mg/kg/hr) corresponds to a rate that is 20% of the maximum Captisol infusion of CAP-fos at pediatric weights. This allows a maximum labeled infusion rate for CAP-fos of 0.4mgPE/kg/min in the pediatric age range. As noted above, this rate is only adequate for CAP-fos infusions administered for short term replacement of oral phenytoin and non-urgent loading dosing.

The PK, Safety & Tolerability references provide support for the total daily Captisol exposure associated with non-urgent loading and maintenance dosing with CAP-fos because the total daily exposure to Captisol in both the voriconazole loading dose phase and maintenance phase exceeds the Captisol exposure associated with the corresponding phases of CAP-fos treatment. The comparative total exposures for CAP-fos and those in the PK, Safety & Tolerability studies are shown in Table 5, Table 6 and Table 7. The shaded columns are titled by relationship to the CAP-fos, or the reference voriconazole treatment. The CAP-fos daily exposure may be compared to the corresponding daily exposures from the voriconazole treatment seen in the references by Walsh et al. (Table 5) and Driscoll et al. (Table 6). There was no loading dose of voriconazole in these two studies. In the study by Walsh et al., the largest proportion of patients with the highest exposure, for the greatest duration, occurred at the 6mg/kg Q12 dose. Therefore, the shaded voriconazole column represents the Captisol exposure values by weight for this dose. In the study by Driscoll et al., all patients received a daily dose of 7mg/kg every 12 hours without a loading dose. The Captisol exposure based on this dose by weight populates the voriconazole column. In Table 7, the comparative Captisol exposures of CAP-fos and those of voriconazole treatment in the study by Mori et al. are shown. The CAP-fos day 1 total dose and subsequent maintenance dosing may be compared to Captisol exposure associated with voriconazole dosing on Day 1 and subsequent maintenance and by age strata.

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Table 2 Literature Reference Support for Pediatric Captisol Dosing from DMF 14364, "Special Populations Report: Captisol use in Pediatric Populations"

<table>
<tr><th>Reference</th><th>Patients (n) Age bands if available</th><th>Dosing</th><th>Duration</th><th>Captisol</th><th>Population</th></tr>
<tr><td>Walsh et al.[1]
Total Patients 48

<table>
<tr><th colspan="3">Patients</th></tr>
<tr><th>Mean age, yrs (SD) [n]</th><th>Cohort 1 N= 24</th><th>Cohort 2 N= 24</th></tr>
<tr><td>2 to <6</td><td>3.7 (1.2) [12]</td><td>2.8 (1.1) [12]</td></tr>
<tr><td>6 to <12</td><td>8.7 (1.9) [12]</td><td>8.1 (1.4) [12]</td></tr>
<tr><td>All</td><td>6.2</td><td>5.4</td></tr>
</table>

<table>
<tr><th colspan="3">Dosing mg (IV)</th></tr>
<tr><th>Treatment Days</th><th>Cohort 1</th><th>Cohort 2</th></tr>
<tr><td>1</td><td>6 x 1</td><td>6 x 1</td></tr>
<tr><td>2 to 4</td><td>4 q12h</td><td>6 q12h</td></tr>
<tr><td>5 to 8*</td><td>6 q12h</td><td>8 q12h</td></tr>
<tr><td colspan="3">Extension up to 20 days</td></tr>
</table>
</td><td></td><td>Maximum 21 Days- see adjacent dosing table</td><td>Rate: 48mg/kg/hour.
0.8mg/kg/min

Total Dose:
Day 1: 192mg/kg
Subsequent days: minimum-96mg/kg/day (see adjacent dosing table)</td><td>Oncology- neutropenia, immune-compromised children (age, 2 to 11 years) at risk for invasive fungal infections.</td></tr>
<tr><th>Reference</th><th>Patients (n) Age bands if available</th><th>Dosing</th><th>Duration</th><th>Captisol</th><th>Population</th></tr>
<tr><td>Driscoll et al.[2]</td><td>Total 40
Ages 2 to 11,
2 to <6 = 24
6 to <12= 16
Mean 5.4 years</td><td>Rate= 3mg/kg/hr

Daily dose 7mg/kg Q12h</td><td>7 days</td><td>Rate: 48mg/kg/hr
0.8mg/kg/min

Total daily dose= 224mg/kg/day</td><td>40 immunocompromised children</td></tr>
<tr><td>Mori[3]</td><td>21 patients

2 to <12 yr = 15
12 to < 15, < 50kg = 4
12 to < 15, ≥50kg = 2</td><td>21 patients received intravenous-to-oral switch regimens: 9 mg/kg of body weight followed by 8 mg/kg of intravenous (i.v.) voriconazole every 12 h (q12h), and 9 mg/kg (maximum, 350 mg) of oral</td><td>target 7 days, maximum 20 days</td><td>Rate:
48mg/kg/hr
0.8mg/kg/min

Total Dose:
Loading IV (day 1)
2 to <12 yr: 288mg/kg,</td><td>Pediatric patients (age 2 to 15 years) requiring treatment for the prevention of systemic fungal infection who were expected to develop neutropenia (defined as absolute neutrophil count, 500 cells/lasting 10 days</td></tr>
</table>

[1] Walsh et al. Pharmacokinetics and Safety of Intravenous Voriconazole in Children after Single- or Multiple-Dose Administration. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2010, p. 4116–4123. doi:10.1128/AAC.00896-10

[2] Driscoll et al. Comparison of Pharmacokinetics and Safety of Voriconazole Intravenous to Oral Switch in Immunocompromised Children and Healthy Adults. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2011, p. 5770–5779. doi:10.1128/AAC.00531-11

[3] Mori M et al. Pharmacokinetics and Safety of Voriconazole Intravenous-to-Oral Switch Regimens in Immunocompromised Japanese Pediatric Patients. Antimicrob Agents Chemother 59:1004 –1013. doi:10.1128/AAC.04093-14.

Reference	Patients (n) Age bands if available	Dosing	Duration	Captisol	Population
	Overall, range 3 to 14 years, mean = 9.2	voriconazole q12h (for patients age 2 to<12 or 12 to<15 years and<50 kg) or 6 mg/kg followed by 4 mg/kg of i.v. voriconazole q12h and 200 mg of oral voriconazole q12h (for patients age 12 to<15 years and>50kg). Rate **3mg/kg/hr**		12 to < 15, ≥50kg: 192mg/kg Maintenance IV, Days 2 to 7: 2 to <12 yr: 256mg/kg/day, 12 to < 15, ≥50kg: 128mg/kg/day	

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Safety Presentation in the Supporting PK, Safety and Tolerability Studies

Study: Walsh et al. (n= 48)

In this study there were two voriconazole dosing cohorts as shown in Table 3, a low and higher dose group.

Table 3 Walsh et al. Voriconazole Intravenous Dosing Cohorts

Dosing mg (IV)		
Treatment Days	**Cohort 1**	**Cohort 2**
1	6 x 1	6 x 1
2 to 4	4 q12h	6 q12h
5 to 8*	6 q12h	8 q12h
*extension up to 20 days		
Dosing mg (PO)		
9 to 11	4 q12h	6 q12h
12	4 q12h	6 q12h

Serious Adverse Events
Eight patients experienced a serious AE during treatment with voriconazole, none of which were assessed by the investigators as treatmentrelated. Ten patients experienced a posttherapy serious AE within 30 days of the last study drug.

Treatment-related adverse events
The most common drug-related AEs were increased cyclosporine concentrations and increased gamma glutamyl transpeptidase (GGTP) levels; visual disturbances were uncommon. Four patients (16.6%) from cohort 1 and nine patients (37.5%) from cohort 2 experienced a treatment-related AE. Of these, two in cohort 1 and five in cohort 2 had hepatic-related events. Eleven patients had mild to moderate treatment-related AEs, while two in cohort 2 experienced severe treatment-related AEs. One, a 5-year-old male, had a serum GGTP concentration increase after 8-mg/kg i.v. dosing. The GGTP values decreased after completion of voriconazole, but at the 1-month follow-up visit they were still abnormal. The second, a 9-year-old girl, experienced severe pruritus on day 4 when she received an i.v. dose of 6 mg/kg. Despite this AE, her dose was escalated to 8 mg/kg according to the study protocol, and the event resolved on day 7.

A single patient from each cohort discontinued study drug due to treatment-related AEs. In cohort 1, a 2-year-old male with normal serum hepatic enzymes and bilirubin at baseline discontinued study drug after 4 days of 4-mg/kg oral suspension due to a voriconazole-related increase of total bilirubin, AST, ALT, and GGTP. At the 1-month follow-up visit, all had decreased to slightly above normal values. In cohort 2, a 2-year-old male with elevated ALT and GGTP values at baseline discontinued the study drug on day 15 of treatment after 5 days of 6-mg/kg oral suspension, due to voriconazole-related hepatic transaminase elevation. At follow-up on day 46, the ALT value had returned to baseline, while the GGTP value was below that recorded at baseline. Three more patients from cohort 1 and five patients from cohort 2 discontinued for reasons not related to the study drug. Among these eight patients, five

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patients withdrew consent; one patient discontinued on day 12 because of tonic seizure, right hemiparesis, and lethargy thought to be related to cyclosporine therapy; one patient with acute myelogenous leukemia and septic shock discontinued after 14 days of 6-mg/kg i.v. voriconazole due to hyperbilirubinemia that was considered to be related to the underlying illness; and the last patient discontinued during the nonpharmacokinetic period because her neutrophil count improved sufficiently to warrant discontinuation of voriconazole therapy.

The authors conclude that the number and type of all-causality AEs were typical for this population; the AE profile was consistent with their underlying conditions and concomitant treatments and was similar to that seen in neutropenic adults. The types of AEs observed in this study were similar to those in the earlier pediatric and adult studies of voriconazole, where most events occurred in three categories: hepatic, cutaneous, and visual.

Reviewer Comment: AEs were consistent with the known AE profile of voriconazole or effects of the serious underlying illness present in the study patients. There is no signal for a differential safety effect to separate the voriconazole-Captisol preparation from the profile of known adverse effects most commonly associated with voriconazole. The adverse effects most likely to be associated with Captisol are renal events. There was no evidence of a renal adverse effect signal to suggest a pediatric intolerance of Captisol.

Study: Driscoll et al. (n= 40)

Serious Adverse Events
No deaths were reported after the start of study treatment. Seventeen subjects experienced 30 serious adverse events (SAEs). The majority of events were attributed to the disease under study, concomitant drug therapy, or concurrent illness. The most commonly reported SAEs were fever (5 subjects), increased ALT (2 subjects), increased AST (2 subjects), cytomegalovirus infection (2 subjects), and graft-versus-host disease (2 subjects). Two SAEs (increased ALT and AST) experienced by one subject during the oral period were assessed as being related to voriconazole. Three SAEs (hypoxia, renal failure, and reversible posterior leukoencephalopathy syndrome) experienced by one subject during the IV and post-IV periods were assessed as being related to both voriconazole and cyclosporine (drug interaction which led to high concentrations of cyclosporine).

Discontinuations
Of the 9 subjects who discontinued the study, 4 discontinued for reasons related to voriconazole (all due to increases in liver function tests). Two subjects temporarily discontinued study treatment due to AEs: one was assessed as being related to methotrexate use, and the other (hypoxia, an SAE) was assessed as being related to both voriconazole and cyclosporine (drug interaction).

Treatment-related adverse events
All 40 subjects experienced all-causality treatment-emergent AEs during the study, and most AEs were mild to moderate in severity. The most common treatment-emergent AEs, reported in at least 20% of subjects in either the IV or oral treatment period, were mucositis, fever, hypertension, pruritus, abdominal pain, rash, increased ALT, increased AST, alopecia, diarrhea, constipation, and fluid retention. These events were often related to accompanying illness and/or concomitant drug or nondrug

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treatments, and the pattern of these events was typical of those expected for subjects with immunosuppression and malignancies. Nine subjects experienced 31 treatment-related AEs, and the most common events were transient elevations of liver function tests. Twenty-six subjects experienced hepatobiliary disorders, and seven subjects experienced 13 treatment-related hepatic AEs.

The authors conclude that the safety and tolerability of voriconazole in children from this study, in terms of hepatic, visual, and cardiac events and laboratory abnormalities, were consistent with the known safety profile of voriconazole in adults. Where differences in the reporting frequencies of AE terms were noted between children and in studies of adults, these could be explained by subjects' underlying conditions or concomitant treatment.

Reviewer Comment: AEs were consistent with the known adverse effect profile of voriconazole or effects of the serious underlying illness present in the study patients. The visual AEs presented in the reference are not included in detail here due to the very specific relationship of this adverse event to voriconazole treatment. There is no signal for a differential safety effect to separate the voriconazole-Captisol preparation from the profile of known adverse effects most commonly associated with voriconazole. The adverse effect most likely to be associated with Captisol are renal events. There was no evidence of a renal adverse effect signal to suggest a pediatric intolerance of Captisol.

Study: Mori et al. (n=21)

Serious Adverse Events
There were no deaths or serious adverse events reported in this study.

Treatment-related adverse events
In total, 18 patients (85.7%) reported 80 all-causality AEs, and 12 patients (57.1%) reported 19 treatment-related AEs. No AEs were reported by 3 patients. No apparent trend in the incidences of AEs was observed by age-weight or CYP2C19 genotype. Two patients discontinued treatment due to AEs (patients 15 and 18 in Table S4 in the supplemental material). One patient had severely abnormal hepatic function (≥2 X the ULN at baseline and ≥5 X the ULN on day 10) and the other had moderately abnormal liver function tests (≥2 X the ULN at baseline and ≥5 X the ULN on day 7 before switching to oral treatment); both events were considered to be related to the study treatment, required treatment, and were confirmed to have resolved after discontinuation of the study treatment. No breakthrough fungal infections were reported.

The most common (incidence, ≥10%) treatment-related AEs were photophobia (9 patients [42.9%]) and abnormal hepatic function (3 patients [14.3%]). There was no correlation between exposure and treatment-related photophobia; however, patients with treatment-related abnormal hepatic function showed relatively higher voriconazole exposures. The majority of AEs were mild to moderate in severity, with 4 patients (19.0%) reporting severe AEs (abdominal pain, increased ALT levels, and oropharyngeal pain [1 patient], febrile neutropenia and epistaxis [1 patient], abnormal hepatic function [1 patient], and sepsis [1 patient]), and 1 patient (4.8%) reporting a treatment-related severe AE (abnormal hepatic function). Excluding the single case of increased ALT level, the severe AEs were confirmed to have resolved.

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As was to be expected from the underlying disease and concomitant treatment, the incidence of hematology test abnormalities was high. The most common nonhematological test abnormalities (incidence, ≥20%) were increases in C-reactive protein (76.2%), gamma-glutamyl transferase (38.1%), AST (28.6%), and ALT (28.6%). No vital sign or electrocardiogram abnormalities were reported as AEs.

The authors conclude the safety profile observed in the pediatric patients in this study using the newly recommended (higher dose) voriconazole regimens raised no further concerns compared with the safety profiles in adults and in previous pediatric studies.

Reviewer Comment: AEs were consistent with the known AE profile of voriconazole or effects of the serious underlying illness present in the study patients. There is no signal for a differential safety effect to separate the voriconazole-Captisol preparation from the profile of known adverse effects most commonly associated with voriconazole. The adverse effect most likely to be associated with Captisol are renal events. There was no evidence of a renal adverse effect signal to suggest a pediatric intolerance of Captisol.

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Table 4 Captisol Infusion Rate in Pediatric Patients for Rapid CAP-fos Loading Dose Compared with the Maximum Rate in Referenced Pediatric PK, Safety & Tolerability Studies of Voriconazole (3mg/kg/hr).

					CAP-fos Associated Captisol Rate				Voriconazole Associated Captisol Rate	
age	kg	Maximum CAP-fos load dose (20mg/kg)	Captisol exposure associated with CAP-fos loading (20mg/kg)	maximum CAP-fos rate, mg/min (LD pediatric max CAP-fos rate 2mgPE/kg/min)	maximum associated Captisol rate, mg/min (pediatric max CAP-fos rate 2mgPE/kg/min)	Voriconazole maximum infusion rate, 3mg/kg/hr (Walsh, Driscoll, Mori)	voriconazole, maximum rate per hour by weight	voriconazole associated Captisol maximum infusion rate/hour by weight	voriconazole associated Captisol maximum infusion rate/minute by weight	voriconazole associated Captisol delivery, proportion of max CAP-fos Captisol Deliver (%)
2	12	240	480	24	48	3	36	576	9.6	20
3	15	300	600	30	60	3	45	720	12	20
4	16	320	640	32	64	3	48	768	12.8	20
5	18	360	720	36	72	3	54	864	14.4	20
6	21	420	840	42	84	3	63	1008	16.8	20
7	23	460	920	46	92	3	69	1104	18.4	20
8	26	520	1040	52	104	3	78	1248	20.8	20
9	28	560	1120	56	112	3	84	1344	22.4	20
10	32	640	1280	64	128	3	96	1536	25.6	20
11	36	720	1440	72	144	3	108	1728	28.8	20
12	40	800	1600	80	160	3	120	1920	32	20
13	46	920	1840	92	184	3	138	2208	36.8	20
14	50	1000	2000	100	200	3	150	2400	40	20
15	56	1120	2240	112	224	3	168	2688	44.8	20
16	61	1220	2440	122	244	3	183	2928	48.8	20

Table 5 Total Captisol Exposure from CAP-fos Treatment Compared to Total Captisol Exposure Identified in the PK, Safety & Tolerability Study by Walsh et al.

					CAP-fos Associated Captisol Exposure		Voriconazole Associated Captisol Exposure (Study = 6mg/kg Q12h for minimum exposure 3 days, n=48; Day 1 Exposure 6mg/kg Q12h followed by 8mg/kg Q12h total 7days, n=24)
age	kg	Cap-fos load dose (20mg/kg)	Captisol exposure at CAP-fos load (20mg/kg)	CAP-fos maintenance dose associated Captisol @ 12 hrs post Loading, maximum 4mgPE/kg	Total Day 1 CAP-fos associated Captisol exposure	"Short Term" Daily maintenance CAP-fos associated Captisol @ 4mgPE/kg Q12 h	Captisol Exposure @ 6mg/kg voriconazole Q12),
2	12	240	480	96	576	192	2304
3	15	300	600	120	720	240	2880
4	16	320	640	128	768	256	3072
5	18	360	720	144	864	288	3456
6	21	420	840	168	1008	336	4032
7	23	460	920	184	1104	368	4416
8	26	520	1040	208	1248	416	4992
9	28	560	1120	224	1344	448	5376
10	32	640	1280	256	1536	512	6144
11	36	720	1440	288	1728	576	6912
12	40	800	1600	320	1920	640	7680
13	46	920	1840	368	2208	736	8832
14	50	1000	2000	400	2400	800	9600
15	56	1120	2240	448	2688	896	10752
16	61	1220	2440	488	2928	976	11712

Table 6 Total Captisol Exposure from CAP-fos Compared to Total Exposure Identified in the PK, Safety & Tolerability Study by Driscoll et al.

					CAP-fos Associated Captisol Exposure		Voriconazole Associated Captisol Exposure
age	kg	CAP-fos loading dose (20mg/kg)	Captisol @ CAP-fos loading (20mg/kg)	CAP-fos maintenance dose associated Captisol @ 12 hrs post Loading, maximum 4mgPE/kg	Total Day 1 CAP-fos associated Captisol	"Short Term" Daily maintenance CAP-fos associated Captisol @ 4mgPE/kg Q12 h	Captisol Exposure @ 7mg/kg voriconazole Q12 x 7 days. n= 40
2	12	240	480	96	576	192	2688

					CAP-fos Associated Captisol Exposure		Voriconazole Associated Captisol Exposure
age	kg	CAP-fos loading dose (20mg/kg)	Captisol @ CAP-fos loading (20mg/kg)	CAP-fos maintenance dose associated Captisol @ 12 hrs post Loading, maximum 4mgPE/kg	Total Day 1 CAP-fos associated Captisol	"Short Term" Daily maintenance CAP-fos associated Captisol @ 4mgPE/kg Q12 h	Captisol Exposure @ 7mg/kg voriconazole Q12 x 7 days. n= 40
3	15	300	600	120	720	240	3360
4	16	320	640	128	768	256	3584
5	18	360	720	144	864	288	4032
6	21	420	840	168	1008	336	4704
7	23	460	920	184	1104	368	5152
8	26	520	1040	208	1248	416	5824
9	28	560	1120	224	1344	448	6272
10	32	640	1280	256	1536	512	7168
11	36	720	1440	288	1728	576	8064
12	40	800	1600	320	1920	640	8960
13	46	920	1840	368	2208	736	10304
14	50	1000	2000	400	2400	800	11200
15	56	1120	2240	448	2688	896	12544
16	61	1220	2440	488	2928	976	13664

Table 7 Total Captisol Exposure from CAP-fos Compared to Total Exposure Identified in the PK, Safety & Tolerability Study by Mori et al.

					CAP-fos Associated Captisol Exposure		Voriconazole Associated Captisol Exposure by Day 1- Maintenance, Age and Weight Strata			
age	kg	CAP-fos loading dose (20mg/kg)	Captisol @ fos load (20mg/kg)	CAP-fos maintenance dose associated Captisol @ 12 hrs post Loading, maximum 4mgPE/kg	Total Day 1 CAP-fos associated Captisol	"Short Term" Daily maintenance CAP-fos associated Captisol @ 4mgPE/kg Q12 h	age 2 to <12 yr & 12 to < 15yr <50kg, Captisol Exposure Day 1, Loading 9mg/kg voriconazole, Q12), n= 19	age 2 to <12 yr & 12 to < 15yr <50kg, Captisol Exposure, Maintenance 8mg/kg voriconazole, Q12) x 2 to 7-day, n= 19	age 12 to < 15yr ≥50kg, Captisol Exposure Day 1, Loading 6mg/kg voriconazole, Q12. n = 2	age 12 to < 15yr ≥50kg, Captisol maintenance exposure Day 2 to 7, 4mg/kg voriconazole, Q12. n= 2
2	12	240	480	96	576	192	3456	3072	1152	1536
3	15	300	600	120	720	240	4320	3840	1440	1920
4	16	320	640	128	768	256	4608	4096	1536	2048
5	18	360	720	144	864	288	5184	4608	1728	2304
6	21	420	840	168	1008	336	6048	5376	2016	2688

					CAP-fos Associated Captisol Exposure		Voriconazole Associated Captisol Exposure by Day 1- Maintenance, Age and Weight Strata			
age	kg	CAP-fos loading dose (20mg/kg)	Captisol @ fos load (20mg/kg)	CAP-fos maintenance dose associated Captisol @ 12 hrs post Loading, maximum 4mgPE/kg	Total Day 1 CAP-fos associated Captisol	"Short Term" Daily maintenance CAP-fos associated Captisol @ 4mgPE/kg Q12 h	age 2 to <12 yr & 12 to < 15yr <50kg, Captisol Exposure Day 1, Loading 9mg/kg voriconazole, Q12), n= 19	age 2 to <12 yr & 12 to < 15yr <50kg, Captisol Exposure, Maintenance 8mg/kg voriconazole, Q12) x 2 to 7-day, n= 19	age 12 to < 15yr ≥50kg, Captisol Exposure Day 1, Loading 6mg/kg voriconazole, Q12. n = 2	age 12 to < 15yr ≥50kg, Captisol maintenance exposure Day 2 to 7, 4mg/kg voriconazole, Q12. n= 2
7	23	460	920	184	1104	368	6624	5888	2208	2944
8	26	520	1040	208	1248	416	7488	6656	2496	3328
9	28	560	1120	224	1344	448	8064	7168	2688	3584
10	32	640	1280	256	1536	512	9216	8192	3072	4096
11	36	720	1440	288	1728	576	10368	9216	3456	4608
12	40	800	1600	320	1920	640	11520	10240	3840	5120
13	46	920	1840	368	2208	736	13248	11776	4416	5888
14	50	1000	2000	400	2400	800	14400	12800	4800	6400
15	56	1120	2240	448	2688	896	16128	14336	5376	7168
16	61	1220	2440	488	2928	976	17568	15616	5856	7808

Reference ID: 4697043

Conclusion: Scientific Rationale for Pediatric Dosing, Bridge to the Published Literature

The listed publications in Table 2 are contained in the Captisol DMF 14364, that was submitted with the Sesquient application, and describe the use of a product that, like Sesquient, contains Captisol as an excipient. It is necessary to rely on these publications to demonstrate the safety of Captisol in the pediatric population, 2 to 16 years of age, for the non-urgent indications proposed for Sesquient (i.e., a non-urgent loading dose and short-term use as a substitute for oral phenytoin). There are no data to support the rate of Captisol administration in any pediatric patients for the proposed SE and urgent loading dose indications. The total dose and rate of administration of Captisol described in these publications support the proposed non-urgent pediatric dosing down to 2 years of age. A total of 109 patients are captured in these studies with an age range that adequately represents the age range of the proposed non-urgent pediatric indications for Sesquient. There were no safety signals identified that were out of alignment with the known safety profile of voriconazole or those expected in the study populations. These publications support the safety of Captisol for non-urgent loading dose or replacement phenytoin therapy indication of Sesquient at a maximum delivery rate of 0.4mgPE/kg/min.

c. CAP-fos IM Dosing and Support for Safety in Adult and Pediatric Patients

The LD allows for IM administration. Similar to IV administration, the safety of Captisol delivery must be supported. Study 247, an adult, healthy volunteer BE study comparing the PK of test product CAP-fos with reference product Cerebyx. The comparison dose was 1000mg fosphenytoin (667 phenytoin equivalents) of each product delivered as 4 x 5ml IM injections. Thus, in the CAP-fos dose of study 247 there was a total of 1334mg Captisol was delivered.

IM Loading Dose of CAP-fos Support from Study 247

If the CAP-fos dose from study 247 is translated to a fraction of an adult loading it would only allow a loading dose up to a maximum patient weight of 33.4 kg. This is due to the maximum Captisol delivery of 1334mg which limits the loading dose to 667mg CAP-fos. When this is divided by the upper limit loading dose of 20mgPK/kg the result is that 33.4 kg is the patient weight limit for a loading dose of bounded by an upper limit of 667mg CAP-fos. If the lower boundary (15mgPE/kg) of the LD labeled fosphenytoin loading dose is chosen, the weight limit is increased to 44.5kg.

IM Maintenance Dose of CAP-fos Support from Study 247

The CAP-fos dose from study 247 may be translated into the upper limit maintenance dose based on the LD label of 6mgPE/kg. This translation would allow a maintenance dose up to a patient weight of 111kg or 244lb. This would allow a maintenance dose for patients in the weight distribution of at least 99.95 of the US population.[4] Study 247 was a single dose study, therefore safety is only supported for a single CAP-fos dose while the LD label indicates that CEREBYX can also be substituted, short-term, for oral phenytoin.

Support for Pediatric IM Use

[4] Mean Body Weight, Height, Waist Circumference, and BMI Among Adults US 1999-2000 through 2015-2016. National Health Statistics Reports, Number 122, December 2018,

Reference ID: 4697043

Review of DMF 14364 does not reveal support for pediatric IM dosing of CAP-fos.
Reviewer Comment: The safety support for IM CAP-fos dosing derived from study 247 is not sufficient for a meaningful approximation to the LD labeling for non-urgent loading or short-term replacement for oral phenytoin. There is no support for pediatric IM use of CAP-fos.

3. CAP-fos Labeling

During review there were two elements of the LD label that could not be included in the CAP-fos label. These are the full indication for treatment of the pediatric population and the allowance for IM dosing. Review of available safety data for the Captisol excipient reveal insufficient data to support the rapid infusion rate of CAP-fos that is required for urgent loading dose in the treatment of SE or seizures occurring during neurosurgery. A reduced maximum rate of CAP-fos infusion rate of 0.4mgPE/kg/min is supported. There is also support for the total Captisol exposure from day 1, loading and maintenance dose, as well as maintenance dosing in short term replacement of oral phenytoin. There is inadequate support for IM CAP-fos dosing for adult or pediatric patients.

4. Conclusions on the Substantial Evidence of Effectiveness and Safety

Effectiveness of Sesquient is supported by the demonstration of a pharmacokinetic bridge to Cerebyx by bioequivalent plasma phenytoin levels. Safety of the total dose and rate of administration of Captisol associated with Sesquient, for treatment of generalized tonic-clonic SE in adults, is supported by reliance on paragraph IV patent certification to Carnexiv. Reliance on information available in the Captisol DMF 14364, for safety of the rate of Captisol infusion associated with Sesquient treatment of SE, is not sufficient to support use in the pediatric population. There is adequate support in DMF 14364 for a reduced maximum rate of CAP-fos infusion rate of 0.4mgPE/kg/min. There is also support for the total Captisol exposure from day 1 loading and maintenance dose, as well as maintenance dosing in short term replacement of oral phenytoin.

Reference ID: 4697043

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/s/

STEVEN T DINSMORE
11/04/2020 09:52:15 AM

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11/04/2020 07:14:10 PM

Clinical Review of Class 2 NDA Resubmission

NDA	210864
SD#	20
Sequence Number	0020
Applicant	Sedor Pharmaceuticals, LLC
Drug	Sesquient (fosphenytoin sodium and sulfobutylether beta-cyclodextrin sodium)
Proposed Indication	Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery. Short term substitution for oral phenytoin
Material Submitted	Class 2 NDA Resubmission
Correspondence Date	6/28/19
Date Received	6/28/19
Date Review Completed	12/5/19
Reviewer	Steven Dinsmore, DO

Review Outline

1. Introduction: Background of captisol-fosphenytoin, 1st submission CR
    a. A Captisol infusion rate of 300mg/minute in adults or 4mg/kg/minute in the pediatric age range must be supported.
2. Resubmission
    a. Clinical- overview of clinical elements, patent certification provided in resubmission
        i. Reference to Carnexiv
            1. Indication- treatment population (adult)
            2. Captisol Exposure Derived from Section 2
            3. Captisol Exposure Derived from sentence 3 and sentence 5 in Section 6.1, under heading: Clinical Trial Experience
            4. Data Corresponding to sentence 3 and sentence 5 from the Carnexiv Clinical Review
        ii. Reference to Vfend
        iii. Reference to DMF 14364, "SPECIAL POPULATIONS REPORT: CAPTISOL® USE IN PEDIATRIC POPULATIONS"
    b. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety
3. Conclusions on the Substantial Evidence of Effectiveness and Safety

1. Introduction

This is a Class 2 resubmission NDA 210864 following a Complete Response on March 22, 2019 because of product quality and clinical safety issues.

Sesquient is a drug product comprised of fosphenytoin sodium and a primary excipient sufobutyl ether beta-cyclodextrin (Captisol®) (b) (4)

(b) (4) room-temperature storage of the drug product at a more physiologic pH of 7(b)(4)–8.2. All other fosphenytoin injection products have a pH specification of 8.3-9.0. Room temperature storage allows improved availability in out-of-hospital emergency situations while the lower pH is more physiologic.

This New Drug Application (NDA) for Captisol-Fosphenytoin relies on the 505(b)(2) regulatory pathway. The proposed indications are identical to those of the fosphenytoin sodium injection Listed Drug (LD) CEREBYX® (Cerebyx) on the basis of two Phase I clinical studies (A98 and 247) that demonstrated pharmacokinetic bioequivalence (BE) to Cerebyx for both intravenous (IV) and intramuscular (IM) administration. No new clinical efficacy study is necessary for the established indications of the LD.

The injectable captisol – fosphenytoin formulation achieved bioequivalence for both intravenous and intramuscular delivery based on studies A98 (IV study) and 247 (IM study), see the Clinical Pharmacology March 15, 2019 Review, of the initial NDA submission.

The safety of the captisol excipient, that is present in a 2 to 1 proportion (Captisol: fosphenytoin) in this formulation, was not established. For the indication of status epilepticus, this formulation delivers Captisol at a rate of 300mg/min. In the initial NDA submission, the applicant relied on the Captisol DMF 14364 (Holder- CyDex Pharmaceuticals, Inc), a literature search, and the body of data from studies A98 and 247 to support the clinical safety of the excipient. None of these sources contained sufficiently comprehensive safety data, frequency of exposure, total exposure or maximum rate of exposure to support the 2400mg total dose of Captisol or the maximum infusion rate of 300mg/min of Captisol that would be delivered during patient treatment for the indication of status epilepticus. There was insufficient support for dosing in the pediatric age range (see Section 7.5.1, Captisol in the initial Clinical Review).

2. Resubmission

This is a Class 2 resubmission following a Complete Response on March 22, 2019. The initial NDA submission failed approval due to product quality issues and insufficient support for the clinical safety of the (b) (4) excipient Captisol at the required delivery rate and total dose for the proposed indication.

Clinical

There is no new clinical efficacy data in this resubmission. Clinical efficacy was adequately supported on the basis of bioequivalent plasma phenytoin levels that provide a pharmacokinetic bridge for Sesquient (captisol-fosphenytoin) to Cerebyx (fosphenytoin).

There are no new clinical safety data for review in this resubmission. In the original submission, safety data from two bioequivalence studies were examined and did not reveal a differential safety signal identified between test (captisol-fosphenytoin) and reference (fosphenytoin) product in the bioequivalence studies, see NDA 210864 initial submission, clinical review.

In the initial submission the applicant strategy to support Captisol clinical safety, as noted in the introduction, relied on DMF 14364 in addition to bioequivalence studies A98 (IV study) and 247 (IM study), and the published literature. Support was found to be insufficient for Captisol at the rate of infusion or total dose required for the Sesquient indication.

In this resubmission, the applicant's strategy to support the safety of the Captisol excipient is to provide a more detailed cross reference to DMF 14364. This DMF was updated in September 2018, during the initial NDA submission review cycle. The update contains two new reports that consolidate relevant data, from within the DMF, on Captisol use in the pediatric population and the renally impaired population. The applicant has also submitted relevant patent certifications for approved products where Captisol is a necessary excipient in the formulation for intravenous delivery. These certifications include paragraph IV[1] patent certification for Carnexiv and a paragraph 2[2] certification for Vfend. The applicant also provides paragraph IV certification for Baxdela and paragraph I[3] certification for Zulresso, however, Baxdela and Zulresso do not add support for adult or pediatric use beyond the support provided by Carnexiv and Vfend. In addition, a search of the Orange Book reveals that Zulresso has 6 drug product patents and one drug use patent entered on June 27, 2019, therefore paragraph 1 certification no longer holds true.

Discussion for support of Captisol in the adult population will be directed at the reference to Carnexiv while for pediatric support the applicant reliance on the Pediatric Special Population report of DMF 14364 and Vfend will be examined.

Reference to Carnexiv

Reference to the Carnexiv label provides support for the use of the Captisol excipient in Sesquient. Carnexiv is indicated for adults.

The Carnexiv label supports Sesquient Captisol infusion rate at three points, the 1st point is in Section 2 "Dosage and Administration", the second and third points of support come from the subheading "Clinical Trial Experience with CARNEXIV" in Section 6.1 "Clinical Trials Experience". These components of the Carnexiv label are shown below:

Carnexiv Label

1 INDICATIONS AND USAGE

CARNEXIV is indicated as replacement therapy for oral carbamazepine formulations, when oral administration is temporarily not feasible, in **adults** with the following seizure types:

- Partial seizures with complex symptomatology
- Generalized tonic-clonic seizures
- Mixed seizure patterns which include the above, or other partial or generalized seizures

Captisol Rate and Total Load derived from Section 2, Carnexiv

2 DOSAGE AND ADMINISTRATION
2.1 Dosage Information

[1] patent invalid, unenforceable, or will not be infringed upon
[2] Patent has expired
[3] The patent information has not been submitted to FDA

The total daily dose of CARNEXIV is 70% of the total daily oral carbamazepine dose from which patients are being switched (see Table 1). The total daily dose of CARNEXIV should be equally divided in four 30-minute infusions, separated by 6 hours.

Table 1 Determination of Total Daily Dose for CARNEXIV Infusion

Total Daily Oral Carbamazepine Dose (mg/day)	Corresponding Total Daily Dose of CARNEXIV (mg/day)	Dose of CARNEXIV to be administered every 6 hours (mg)
400	280	70
600	420	105
800	560	140
1,000	700	175
1,200	840	210
1,400	980	245
1,600	1,120	280

Analysis of Captisol exposure derived from Carnexiv label, Section 2: Based directly on Carnexiv administration from Section 2, the maximum dose of carbamazepine is 1600mg /day. When provided as Carnexiv this equals 1120mg/day. This results in a maximum delivery of 280mg Carnexiv at each dose interval. This dose of 280mg Carnexiv is coupled with 7000mg of Captisol. When delivered over the recommended infusion rate of 30 minutes, this yields a Captisol deliver rate of **233mg/min with a total daily Captisol load of 28,000mg**. As a comparison, Sesquient treatment for status epilepticus results in delivery of Captisol at a rate of 300mg/min.

Captisol Total Load and Maximum Rate Derived from Section 6.1, "Clinical Trial Experience with CARNEXIV", Sentence 3 and 5.

Section 6.1:

Clinical Trial Experience with CARNEXIV
The data described below are based on an open-label 7-day study with CARNEXIV in 98 patients, and an open-label 5-day study with CARNEXIV in 105 patients. All infusions were administered in equally divided doses given separately every 6 hours. *Of the 203 patients in the studies, 160 received multiple 15-minute infusions and 43 received multiple 30-minute infusions.* Most patients received a total daily intravenous dose ranging from 280 mg to 1,120 mg (equivalent to total daily oral dose of 400 mg to 1,600 mg) in divided doses given every 6 hours. *Eight patients received up to 1,400 mg total daily intravenous dose (equivalent to total daily oral dose of 2,000 mg).*

Analysis of Carnexiv Label Support, Section 6.1

Sentence 3: "Of the 203 patients in the studies, 160 received multiple 15-minute infusions and 43 received multiple 30-minute infusions."

Sentence 3 of "Clinical Trial Experience with CARNEXIV" in Section 6.1 reads as follows: "*Of the 203 patients in the studies, 160 received multiple 15-minute infusions and 43 received multiple 30-minute infusions.*" Based on this sentence in isolation, the total daily dose of Carnexiv each patient received is

not known. It is only known that, to participate in a study that supported the current label, the dose range for these patients was between 400mg and 1600mg carbamazepine a day or 280 to 1120mg Carnexiv a day. If we consider the 15-minute infusion cohort, this yields Captisol infusions that have a potential maximum infusion rate from 116 mg/min to 466 mg/min. However, the distribution of the 160 patients across these infusion rates is not known. It may be inferred that at least one patient achieved a rate of 466mg/min of Captisol. It is also not known, based on the sentence from the label, how many of the 160 patients had Captisol infusion rates between 300mg/min and 466mg/min.

Corresponding Data from Carnexiv Review

ACTUAL DATA- from Carnexiv review for sentence 3: from among the 15-minute infusion cohort there were 122 patients that received a total of 400 Carnexiv infusions that delivered Captisol at a rate greater than 300mg/minute. There were 115 patients that received 316 infusions that delivered Captisol at 350mg/min or greater, see Table 2. From among the overall 160 patients in the 15-minute infusion cohort, there were 631 infusions with a mean Captisol infusion rate of 346mg/min.

Table 2 Carnexiv 15-minute infusion cohort, Captisol infusion rate, total infusions, total Captisol, number of patients

Daily IV CBZ (mg)	CBZ / infusion (mg)	Captisol / infusion (mg)	**Captisol mg/min**	**Total IV Infusions (per patient)**	**Number of Patients**	Daily Captisol (grams)	Total Captisol Study Exposure (grams)
1400	350	8750	583	28	1	35	245
1400	350	8750	583	12	2	35	105
1260	315	7875	525	28	1	32	221
1260	315	7875	525	12	3	32	95
1120	280	7000	467	28	6	28	196
1120	280	7000	467	12	14	28	84
1110	277.5	6938	463	12	1	28	83
1050	262.5	6563	438	28	1	26	184
1050	262.5	6563	438	28	1	26	184
1050	262.5	6563	438	12	4	26	79
980	245	6125	408	28	2	25	172
980	245	6125	408	12	6	25	74
951	237.75	5944	396	12	1	24	71
910	227.5	5688	379	12	1	23	68
840	210	5250	350	28	6	21	147
840	210	5250	350	12	62	21	63
840	210	5250	350	7	2	21	37
840	210	5250	350	5	1	21	26
838	209.5	5238	349	12	1	21	63
835	208.75	5219	348	12	1	21	63
835	208.75	5219	348	12	1	21	63
831	207.75	5194	346	12	1	21	62
825	206.25	5156	344	12	1	21	62
823	205.75	5144	343	12	1	21	62
815	203.75	5094	340	12	1	20	61
700	175	4375	292	28	4	18	123
630	157.5	3938	263	28	4	16	110
560	140	3500	233	28	8	14	98
560	140	3500	233	24	1	14	84
420	105	2625	175	28	1	11	74
420	105	2625	175	28	9	11	74
350	87.5	2188	146	28	1	9	61
304	76	1900	127	10	1	8	19
280	70	1750	117	28	8	7	49
64	16	400	27	1	1	2	0
			Mean Captisol infusion rate 346mg/min	Total infusions, 631	Total patients, 160		

Reviewer Comment, Sentence 3: When maximum Captisol total daily load and maximum rate are derived from the language of sentence 3, there is at minimum, a single patient that received Captisol at 466mg/min with a maximum total daily load of 28,000mg. The actual study data from Carnexiv reveal there were 115 patients that received 316 Carnexiv infusions (doses) that delivered Captisol at 350mg/min or greater with total daily Captisol loads ranging from 20,000mg to 35,000mg. These data

provide a wide safety support margin for the Captisol delivery that is coupled with the proposed Captisol-fosphenytoin product.

Sentence 5: *"Eight patients received up to 1,400 mg total daily intravenous dose (equivalent to total daily oral dose of 2,000 mg)."*

Based on sentence 5 of "Clinical Trial Experience with CARNEXIV" in Section 6.1, *Eight patients received up to 1,400 mg total daily intravenous dose (equivalent to total daily oral dose of 2,000 mg)* " it is implied that 8 patients received between 1121mg and 1400mg Carnexiv. It is not known from the label how many patients received 1400mg. It is only certain that one patient received the maximum 1400mg of Carnexiv. This hypothetical, single patient, then received 8750mg of Captisol over 30 minutes, if given at the labeled rate. This equals **292mg/min** of Captisol. The most conservative inference from the sentence is that one patient reached a 1400mg total dose. The remaining patients may have received less, the distribution of exposures between the labeled maximum total dose of 1120mg Carnexiv a day (equal to Captisol 233mg/min) and the upper limit of 1400mg Carnexiv a day (equal to Captisol 292mg/min) is uncertain.

ACTUAL DATA- from the Carnexiv review for sentence 5: These 8 patients had total daily doses ranging from 1260mg to 1400mg where 4 patients had a 1400mg daily dose. These patients had 84 infusions ranging from 525mg/min of Captisol to 1750mg/min, see Table 3.

Table 3 Eight Patients with total daily Carnexiv dose >1120mg/day up to 1400mg day from Carnexiv Clinical Review

Daily IV CBZ (mg)	CBZ / infusion (mg)	Captisol / infusion (mg)	**Captisol mg/min**	**Total IV Infusions (per patient)**	**Number of Patients**	Daily Captisol (grams)	Total Captisol Study Exposure (grams)
5 Minute Infusion							
1400	350	8750	1750	4	1	35	35
15 Minute Infusion							
1400	350	8750	583	28	1	35	245
1400	350	8750	583	12	2	35	105
1260	315	7875	525	28	1	32	221
1260	315	7875	525	12	3	32	95

Reviewer Comment, sentence 5: When maximum Captisol total daily load and maximum rate are derived from the language of sentence 5, there is at minimum one patient that received Captisol at a maximum rate of 292mg/min with a maximum total daily load of 35,000mg. The actual study data from Carnexiv reveal there was one patient that received 4 Carnexiv infusions (doses) that delivered Captisol at a maximum rate of 1750mg/min with a total daily Captisol load of 35,000mg. There were 3 patients that received 40 Carnexiv infusions (doses) that delivered Captisol at a maximum rate of 583mg/min with total daily Captisol load of 35,000mg. There were an additional 4 patients that received 40 Carnexiv infusions (doses) that delivered Captisol at a maximum rate of 525mg/min with total daily Captisol load of 32,000mg. These data provide a wide safety support margin for the Captisol delivery that is coupled with the proposed Captisol-fosphenytoin product.

Conclusion: Reference to Carnexiv provides support for the rate and total dose of the excipient Captisol delivered by the Sesquient when used for all treatment indications in adults. Carnexiv does not provide support for the pediatric population.

Reference to Vfend

Vfend is an antifungal product that has an intravenous formulation. The intravenous formulation also contains Captisol. Vfend is indicated for use in patients 12 years of age and older. Although Vfend has an indication for a pediatric population subset, reference to this product does not provide support for a partial pediatric indication for Sesquient because the rate of Captisol infusion is lower than the rate needed to support Sesquient infusion. Table 4 below shows that the maximum rate of Captisol infusion during Vfend treatment is 20% of the maximum rate of Captisol infusion during Sesquient treatment of status epilepticus (column 9 of Table 4). Therefore, reference to Vfend dose not provide support for the rate of Captisol infusion in any population, including the 12 year to 16-year, pediatric age range. Reference to Vfend provides support only for the total dose of Captisol delivered by Sesquient in the pediatric age range. In the case of total dose, the day 1 dose of Captisol associated with Vfend treatment is 370% of the total day 1 dose associated with Sesquient treatment (Table 4, column 11).

Table 4 Captisol Maximum Rate and Total Dose, Sesquient Compared to Vfend

1	2	3	4	5	6	7	8	9	10	11
age	kg (wt, males, 50%)	Sesquient load dose (20mg/kg)	Total Captisol at Sesquient load (20mg/kg)	max Sesquient captisol rate, mg/min	Vfend load (mg), 1st dose	Vfend total Captisol Deliver day 1 (6mg/kg X2)	Vfend max Captisol rate/min by weight	Vfend % of max Sesquient - Captisol delivery/minute by weight	Sesquient -Captisol load, day 1 with follow on maintenance dose	Vfend day 1 % of Max total Sesquient day 1, Captisol load
12	40	800	1600	160	240	7680	32	20	2080	370
13	46	920	1840	184	276	8832	37	20	2392	370
14	50	1000	2000	200	300	9600	40	20	2600	370
15	56	1120	2240	224	336	10752	45	20	2912	370
16	61	1220	2440	244	366	11712	49	20	3172	370

Reviewer Comment: Reference to Vfend does not provide support for use of Sesquient in the pediatric age range due to absence of parity in rate of Captisol infusion (20% of Sesquient). The Vfend total day 1 Captisol dose is 3.7 times the Captisol present in the day 1 dose of Sesquient and thus adequately supports total only total dose.

Reference to DMF 14364, SPECIAL POPULATIONS REPORT: CAPTISOL® USE IN PEDIATRIC POPULATIONS

DMF review

Examination of the prospective studies reveals that none are directed specifically at Captisol, only an associated API. The DMF holder concedes "that prospective clinical trials provide the best data but are limited for pediatric administration of Captisol."

The examination of prospective studies that use an IV delivery method, identified by in the Pediatric study report, does not provide the infusion rate of study drug, which is usually voriconazole. The safety data provided in these studies is summary data that is often admixed with the success of treatment with the active pharmaceutical ingredient. In the short safety presentations, the findings relevant to Captisol are eclipsed by severe underlying illness, effects of the active drug, and concomitant medications.

Examination of the retrospective studies reveals similar limitations to the prospective studies. These studies are also limited by the retrospective collection of safety data from medical records. The Infusion rates of Captisol associated drugs are not provided, thus comparison with Sesquient labeled infusion rate cannot be performed. The safety data provided in these studies is summary data that is often admixed with the success of treatment of the active pharmaceutical ingredient. In the short safety presentations, the findings relevant to Captisol are eclipsed by severe underlying illness, effects of the active drug and concomitant medications.

Review of material from publicly available sources included the medical literature and postings in CliinicalTrials.gov and EudraCT. There were 91 Literature references provided in the DMF, linked to the pediatric study report and PK study reports. These were examined for content that may be supportive of the Sesquient rate of infusion or total dose for the pediatric population. These studies include those identified above as "prospective" and "retrospective" studies. None of these have rate of infusion and safety data is limited as noted in the discussions above of the prospective and retrospective studies.

CyDex, the DMF holder includes a discussion of 5 trials identified in ClinicalTrials.gov. All of these studies were of voriconazole treatment. Only one of the studies includes the voriconazole dose. None include rate of infusion, and all have only a brief safety summary data. The EudraCT database reveals five studies that include drug dosing that allows measure of the Captisol load. However, none of the study synopses includes the rate of voriconazole infusion. Safety data has the shortcomings noted in the above discussions of the prospective and retrospective studies.

Reviewer Comment: The CyDex Pediatric Special Population report identifies extensive exposure to Captisol in the pediatric population, primarily associated with the use of voriconazole. However, the information provided does not rise to the level of evidence necessary to support the use of this excipient in the pediatric population. This is because the Captisol infusion rate is not provided. Voriconazole may be delivered at the labeled rate in the referenced studies that were captured by the special populations report. This is not stated explicitly. If delivered at the labeled rate, at any pediatric weight, the infusion is not greater than 20% of the rate of Captisol infusion associated with Sesquient. In addition, the safety data in the reports is limited to summary information and any safety effect of Captisol is eclipsed by the active pharmaceutical ingredient and the underlying medical illness.

Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

CMC: (b) (4) particulate material has been identified in the CE-fosphenytoin product. A teleconference was held with the applicant on 11/7/2019 during which it was determined that the source of the particulates was not identified and that a solution to eliminating this impurity was not yet available. (b) (4) (b) (4) This is an untenable corrective measure in an emergency use situation, such as status epilepticus. Likewise, in settings that are not as time sensitive, such as inpatient phenytoin replacement therapy, there is no medical need for this product due to the availability of refrigerated fosphenytoin.

3. Conclusions on the Substantial Evidence of Effectiveness and Safety

Effectiveness of Sesquient is supported by the demonstration of a pharmacokinetic bridge to Cerebyx by bioequivalent plasma phenytoin levels. Safety of the total dose and rate of administration of Captisol associated with Sesquient, for treatment of generalized tonic-clonic status epilepticus in adults, is supported by reliance on paragraph IV patent certification to Carnexiv. Reliance on publicly available sources, peer-reviewed published literature, and information available in the Captisol DMF 14364, for safety of the rate of Captisol infusion associated with Sesquient treatment of status epilepticus, is not sufficient to support use in the pediatric population.

The product cannot be recommended for approval due to the presence of (b) (4) particles in the Sesquient product.

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/s/

STEVEN T DINSMORE
12/20/2019 02:26:55 PM

PHILIP H SHERIDAN
12/20/2019 02:29:17 PM

Cross-Discipline Team Leader Review

Date	3/15/2019
From	Angela Yuxin Men, MD., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA#	NDA 210864
Applicant	Sedor Pharmaceuticals, LLC
Date of Submission	May 22, 2018
PDUFA Goal Date	March 22, 2019
Proprietary/ Established (USAN) Name	SESQUIENT (Captisol-enabled fosphenytoin sodium Injection)
Dosage forms / Strength	Solution for intravenous (IV) or intramuscular (IM); (b) (4) 10ml vial and both at a concentration of 50 mg PE/mL
Proposed Indication(s)	Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
Recommended:	Complete Response

1. Introduction

Sedor Pharmaceuticals LLC (Sedor) submitted New Drug Application # 210864 for Captisol®-Enabled Fosphenytoin Sodium Injection (CE-Fosphenytoin) via the 505(b)(2) regulatory pathway. The applicant is relying on the FDA's finding of safety and effectiveness for Cerebyx (NDA 020450), the listed drug (LD), and is seeking the same indication approved for Cerebyx: treatment of generalized tonic-clonic status epilepticus (SE) and for the prevention and treatment of seizures occurring during neurosurgery. CE-Fosphenytoin also can be substituted, as short-term use, for oral phenytoin.

Currently, the LD Cerebyx, needs to be stored under refrigeration at 2°C to 8°C (36°F to 46°F). This product should not be stored at room temperature for more than 48 hours (Cerebyx Prescribing Information, Pfizer Inc, 2017). CE-Fosphenytoin is a drug product comprised of a primary excipient sulfobutyl ether beta-cyclodextrin (i.e., Captisol®) (b) (4) room-temperature storage of the drug product at a more physiologic pH of 7(b) (4)–8.2.

Fosphenytoin is a pro-drug that is rapidly converted to the active drug phenytoin in blood; therefore, the fosphenytoin concentration in marketed fosphenytoin sodium injection products is expressed as milligrams of phenytoin equivalents (PE)/mL rather than as mg/mL. The fosphenytoin sodium formulation of 75 mg/mL is equivalent to 50 mg phenytoin sodium equivalents (PE)/mL following parenteral administration.

Sedor submitted Chemistry, Manufacturing, and Control (CMC) information, two pivotal bioequivalence (BE) studies which compared CE-Fosphenytoin to Cerebyx: Study 20-A98-AU (CE-Fosphenytoin Versus Cerebyx® After IV Administration) and Study 20-247-SA (CE-Fosphenytoin Versus Cerebyx® After IM Administration), and what it believes sufficient

safety information for the primary excipient Captisol (sulfobutyl ether betacyclodextrin) to support approval.

The following are the key primary reviewers for the SESQUIENT NDA:

CDTL: Angela Men		
RPM: Heather Bullock	**CPMS**: Jackie Ware	
ADRA: Colleen Locicero		
Discipline	**Reviewer**	**TL**
Clinical	Steve Dinsmore	Phil Sheridan
Pharm/Tox	Ed Fisher	Lois Freed
Product Quality (OPQ CMC)	DS: Mouli (Sithamalli Chandramouli) DP: Andrei Ponta EA: Andrei Ponta	ATL: Martha Heimann
	Process: Peter Krommenhoek Facility: Peter Krommenhoek	
	RBPM: Dahlia Walters	
Clinical Pharm	Hristina Dimova	Angela Men
OSIS BEQ	Consult submitted	Shila Nkah (RPM)
OSE	PM: Monique Killen	
OSE/DMEPA	Chad Morris	Lolita White
OSE/DRISK	N/A	N/A
OSE/DEPI	Elisa Braver	Kira Leishear White
	Karen Long	Allen Brinker
CSS	TBD: Martin Rusinowitz	
	PM: Sandy Saltz	
Labeling	ADL: Tracy Peters	
OPDP	Dhara Shah	Aline Moukhtara

2. Regulatory Background

CyDex Pharmaceuticals originally filed IND 74871 on September 24, 2007. Ligand Pharmaceuticals acquired CyDex on January 26, 2011. Subsequently, Sedor acquired the rights to license CE-Fosphenytoin on December 7, 2015.

A Pre-NDA meeting was held on July 6, 2017. The Agency evaluated the applicant's plans to submit an NDA for CE-Fosphenytoin Injection, and investigated the information provided regarding prior concerns raised by the Division in the June 3, 2016, correspondence regarding the CMC development of the product and safety concerns related to the Captisol present in the drug product. Specifically, the Agency clearly reiterated that the applicant would need to support the safety of the proposed dose, maximal concentration, and infusion rate for Captisol in its product. This issue had been raised in the development program as early as a pre-IND meeting held in 2006. It was noted that the applicant could choose to attempt to provide this

support by appropriately referencing approved Captisol-containing products that it believed were relevant to its planned marketing application. If the applicant elected to take such an approach, appropriate comparisons with the no observed adverse effect levels (NOAELs) for Captisol observed in nonclinical studies (rat and dog) would also need to be made.

The NDA was submitted on May 22, 2018 and was reviewed on a standard 10-month review clock.

3. CMC

The Office of Product Quality (OPQ) review team recommends that the Agency issue a Complete Response Letter for NDA 210864 for Sesquient® (fosphenytoin sodium) injection. From a quality perspective, the application does not include adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use to treat the intended patients. There are six deficiencies that were conveyed to the applicant in a CMC Discipline Review (DR) Letter dated 2/26/2019. By the time of this review, Sedor only submitted CMC information on March 14th providing responses to the CMC review team's identified deficiencies # 3, 4, and 5 (see below) and no responses for deficiencies #1, 2, and 6 (see below). The CMC review team has determined that the inability of the applicant to adequately respond to the deficiencies outlined in the DR Letter does not permit for a review during the current cycle and should result in a Complete Response action.

CMC deficiencies that were conveyed to the applicant in the February 26, 2019, CMC Discipline Review letter are listed below:

1. Validate and provide validation results for the assay, identification, and impurity analytical method with respect to related substances. In a response to an information request dated 16-Nov-2018, you indicated that the assay, identification, and impurity analytical method was not validated for related substances. This is not acceptable as the accuracy of the results for related substances provided to date cannot be assured.

2. As the analytical method used to quantify impurities and related substances has not been adequately validated at this time, the shelf-life for the drug product cannot be determined. The validity of the reported content for related substances cannot be confirmed as the analytical method is not validated for related substances.

3. The proposed prescribing information includes a statement that the drug product is to be diluted with either 5% dextrose or 0.9% saline to a concentration ranging from 1.5 mg PE/mL to 25 mg PE/mL. Adequate product quality information was not submitted to support this labeling instruction, as noted below.

   a. Provide data demonstrating that the drug product is stable at concentrations of 1.5 mg PE/mL and 25 mg PE/mL. The compatibility study was performed at a concentration of 7.5 mg fosphenytoin sodium/mL (5 mg PE/mL) and 15 mg fosphenytoin sodium /mL (10 mg PE/mL). The submitted data does not support the dilution concentration range proposed in the labeling instruction.

   b. Provide data demonstrating that the drug product is stable in 5% dextrose. The compatibility study was only performed using 0.9% sodium chloride. Ensure that data includes information for 1.5 mg PE/mL and 25 mg PE/mL concentrations.

c. Provide a description and validation package for the analytical method used to determine assay and related substances for the compatibility study. It is unclear from the submitted information if the same proposed regulatory analytical method was used for analysis of compatibility study samples.

4. As noted in our information requests from June 22, 2018, our discussion in the meeting from July 6, 2017, our response to Question 9 of the Type C Meeting dated June 3, 2016, and our response to Question 1 of the pre-IND meeting dated September 20, 2006, the proposed product does not comply with the USP Monograph for Fosphenytoin Sodium Injection. As previously advised, we encourage you to contact USP with respect to possible revisions to the current monograph that would enable compliance for your product. Revisions are needed for acceptance criterion for both pH and phenytoin impurity limit. Please refer to the following USP website for information regarding guidelines for submitting requests for revision to the USP-NF through the pending monograph process (http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/pendingStandards/2015-06- 01-pending-monograph-guideline.pdf).

5. We could not locate in-process control testing results for all manufacturing stages for your registration batches in Module 3.2.P.3.4. We recommend that you submit the results in a tabular format. If you have submitted this information earlier, please indicate its exact location.

6. Describe the risk mitigation strategies in your manufacturing process to control the presence of (b) (4) particles.

4. Nonclinical Pharmacology/Toxicology

The nonclinical information for fosphenytoin was reviewed under the Cerebyx NDA (NDA 20450), the LD for the current application. The local tolerance study in rat and the most relevant toxicity information contained in the Captisol Drug Master File (DMF) are reviewed in this review cycle.

To support the safety of a 505(b)(2) application for a new formulation of fosphenytoin to be used on a short-term basis in epilepsy, the applicant conducted a local toxicity study in rats and referred to the DMF for Captisol (sulfobutyl ether beta-cyclodextrin; CAP), the primary excipient used in the new formulation. Based on the results of the intramuscular local toxicity study in the rat using the clinical formulation, there was no evidence of excipient-related local toxicity. The toxicity of IV bolus and continuous infusion of Captisol has been characterized in rat, dog, and monkey studies conducted by the manufacturer (Cy-Dex).

The nonclinical data provided in the current application and available in the Captisol DMF, for which a LOA was provided, are considered adequate to support administration of CE-fosphenytoin at the maximum rate and total daily dose of Captisol proposed for adults. They, however, do not substitute for human safety data. Additionally, the juvenile animal toxicology study of Captisol (contained in the DMF) is inadequate by design to support initiation of clinical studies or marketing approval for pediatric patients less than 12 years of age.

5. Biopharmaceutics

N/A

6. Clinical Pharmacology

The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 210864 and finds it acceptable from an OCP perspective.

The clinical program included two pivotal bioequivalence (BE) studies to compare CE-Fosphenytoin to Cerebyx: Study 20-A98-AU (CE-Fosphenytoin Versus Cerebyx® After IV Administration) and Study 20-247-SA (CE-Fosphenytoin Versus Cerebyx® After IM Administration). Bioequivalence (in terms of plasma phenytoin levels) was demonstrated in both studies, establishing clinical bridge for CE-Fosphenytoin versus Cerebyx.

BE studies inspection request was sent to the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS). They determined that an inspection is not warranted at this time for the sites listed.

7. Efficacy

There is no clinical efficacy trial conducted.

8. Safety

There is lack of adequate information to support the safety of the excipient (b) (4) Captisol® in the SESQUIENT formulation. Overview of the product ingredients is listed below.

Ingredients	Concentration	Composition (b) (4) Vial 10 mL	Function
Active Substances(s)			
Fosphenytoin Sodium	75mg/mL[1]	(b) (4)	Active ingredient
Excipients			
Captisol	100 mg/mL		(b) (4)

*2ml fill volume

[1]equivalent to 50 mg phenytoin sodium

A primary use of fosphenytoin is treatment of status epilepticus. Fosphenytoin may also be used for short-term phenytoin maintenance therapy when oral phenytoin administration is not possible. An adult loading dose of fosphenytoin is 15 to 20 mg PE/kg at a rate of 100 to 150 mg/min while a pediatric loading dose is 15 to 20 mg PE/kg at a rate of 2 mg PE/kg/min or 150 mg PE/ min, whichever is slower. An adult loading dose for a 60 kg individual would deliver a total Captisol dose of 2400 mg at a rate of 300 mg/min.

The applicant clearly indicates that they are relying only on the clinical safety data from the PK studies provided in the application, published literature provided in the application, and on DMF # 14364 (CyDex Pharmaceuticals, Inc.) to attempt to support the clinical safety of the excipient Captisol. The clinical review team determined that the information in DMF # 14364 and published literature do not contain either sufficiently comprehensive safety data, dosing

frequency, total exposure, and/or a maximum rate of exposure to support the safety of Captisol in the applicant's product for the proposed indications in any age group. Additionally, the clinical review team concludes that the Captisol safety data from the IV PK study conducted with the current application are inadequate in terms of dosing frequency, total dose, and infusion rate to support the applicant's proposed indications (it should be noted that Captisol PK data was not obtained in that trial). The clinical review team therefore recommends that a Complete Response action be taken.

The Division of Pediatrics and Maternal Health (DPMH) was involved in the review of this application as the applicant proposes dosing in pediatric patients. The DMPH reviewer ultimately defers to the nonclinical, clinical, and clinical pharmacology review teams with specific respect to the assessment of the safety of Captisol in the proposed products in pediatric age groups. For the reasons outlined above in this memo, the approval of this application is not supported, in part, because the applicant has not adequately supported the safety of the proposed exposure to Captisol in its product in any age group, including pediatric patients.

9. Controlled Substance Staff

Regarding Controlled Substance Staff, based on their review of Cerebyx's and Dilantin(phenytoin)'s original NDAs, along with the published medical literature for more than the last 65 years, CE-Fosphenytoin does not have any abuse-related concerns.

10. Labeling

DMEPA found the proprietary name, SESQUIENT, acceptable from both a promotional and safety perspective. They identified areas of the proposed labels and labeling where information can be improved or added to help ensure the safe and effective use of this product. However, the above identified CMC deficiencies and safety issues preclude discussion of labeling changes and/or post-marketing requirements/commitments at this time. There is no labeling negotiation during this review cycle.

11. Recommended Regulatory Action

The applicant's submission has numerous CMC deficiencies. Additionally, the applicant has not established the safety of the proposed exposure to Captisol in its product for the proposed indications. Therefore, this application does not provide adequate information for regulatory approval of SESQUIENT. A Complete Response should be issued for NDA 210864.

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/s/

YUXIN MEN
03/20/2019 12:15:48 PM

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210864
Priority or Standard	Standard
Submit Date(s)	5/22/18
Received Date(s)	5/22/18
PDUFA Goal Date	3/22/19
Division/Office	OND1/DNP
Reviewer Name(s)	Steven Dinsmore, DO
Review Completion Date	2/22/2019
Established/Proper Name	fosphenytoin sodium
(Proposed) Trade Name	Sesquient
Applicant	SEDOR PHARMACEUTICALS
Dosage Form(s)	intravenous or intramuscular use.
Applicant Proposed Dosing Regimen(s)	Status Epilepticus: Adult loading dose is 15 to 20 mg PE/kg at a rate of 100 to 150 mg PE/min; Pediatric loading dose is 15 to 20 mg PE/kg at a rate of 2 mg PE/kg/min (or 150 mg PE/min, whichever is slower) Non-emergent Loading and Maintenance Dosing: Adult loading dose is 10 to 20 mg PE/kg given IV or IM; initial maintenance dose is 4 to 6 mg PE/kg/day in divided doses; Pediatric loading dose is 10 to 15 mg PE/kg at a rate of 1 to 2 mg PE/kg/min; initial maintenance dose is 2 to 4 mg PE/kg every 12 hours at a rate of 1 to 2 mg PE/kg/min (no faster than 100 mgPE/min)
Applicant Proposed Indication(s)/Population(s)	Indication: treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery as well as short-term substitution for oral phenytoin when oral administration is not possible. Population: Adults and Pediatrics from birth to <17 years
Recommendation on Regulatory Action	The proposed product cannot be approved due to insufficient safety data to support the administration rate and total dose of the excipient Captisol
Recommended Indication(s)/Population(s) (if applicable)	Labeling recommendations cannot be made

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Glossary

247	IM Sesquient to IM Cerebyx BE study 20-247-SA
A98	IV Sesquient to IV Cerebyx BE study 20-A98-AU
AE	adverse event
AR	adverse reaction
BA	Study Sequence, A = test product, B= reference product
AB	Study Sequence, A = test product, B= reference product
BE	Bioequivalence
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMF	Drug Master File
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
IM	intramuscular
IND	Investigational New Drug Application
IV	intravenous
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
OORR	out of reference range
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PE	phenytoin equivalents
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act

REF	reference product -fosphenytoin (treatment B)
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
TEAE	treatment emergent adverse event
TEST	test product, Captisol - fosphenytoin (treatment A)

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1. Executive Summary

1.1. Product Introduction

This is a drug product comprised of fosphenytoin sodium and a primary excipient sufobutyl ether beta-cyclodextrin (Captisol®) (b) (4) room-temperature storage of the drug product at a more physiologic pH of 7(b) (4)–8.2. This would be an advantage over currently approved fosphenytoin sodium injection products which require storage under refrigerated conditions and are thus not as readily available to first responders.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This New Drug Application (NDA) for Captisol-Fosphenytoin is reliant on the 505(b)(2) regulatory pathway. The proposed indications are identical to those of the fosphenytoin sodium injection Reference Listed Drug (RLD) CEREBYX® (Cerebyx) on the basis of two Phase I clinical studies (A98 and 247) that demonstrated pharmacokinetic bioequivalence (BE) to Cerebyx for both intravenous (IV) and intramuscular (IM) administration. No new clinical efficacy study is necessary for the established indications of the LD.

Although the injectable captisol – fosphenytoin formulation has achieved bioequivalence for both intravenous and intramuscular delivery based on studies A98 (IV study) and 247 (IM study) the safety of the captisol excipient that is present in a 2 to 1 proportion (Captisol: fosphenytoin) in this formulation has not been established. The applicant has relied on the Captisol DMF # 14364, a literature search, and the body of data from studies A98 and 247 for the clinical safety of the excipient. None of these sources contains sufficiently comprehensive safety data, frequency of exposure, total exposure or maximum rate of exposure to support the 2400mg total dose of Captisol or maximum infusion rate of 300mg/min of Captisol that are delivered for the indication of status epilepticus or to support dosing in the pediatric age range (see Section 7.5.1, Captisol).

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Bioequivalence to the listed drug was established for intravenous and intramuscular administration in studies A98 and 247 respectively. This establishes a bridge to rely on the findings for safety and efficacy of the fosphenytoin sodium listed drug CEREBYX®. The need for a 505b2 pathway is based on the change in formulation for the proposed drug that contains a different quantity of excipients than the listed drug.[1] This excipient, Captisol, is present in the proposed formulation in a 2:1 proportion (Captisol 2mg : fosphenytoin 1mg PE). The formulation will deliver an excipient, not present in the listed drug. (b) (4) (b) (4) room temperature storage of the drug product at a more physiologic pH of 7 (b) (4) –8.2. All other fosphenytoin sodium injection products require storage under refrigeration with a pH specification range of 8.6-9.0. This would allow greater availability of fosphenytoin treatment where cold chain may be interrupted such as first responder vehicles. This might allow fosphenytoin to be given earlier in the course of status epilepticus before the patient becomes more refractory to therapy.

Captisol will be infused at a rapid rate when delivered for the indication of status epilepticus. A primary use of fosphenytoin is treatment of status epilepticus due to the ability to rapidly deliver a therapeutic loading dose of phenytoin. Fosphenytoin may also be used for short term phenytoin maintenance therapy when oral phenytoin administration is not possible. An adult loading dose of fosphenytoin is 15 to 20mgPE/kg at a rate of 100 to 150mg/min while a pediatric loading dose is 15 to 20mgPE/kg at a rate of 2mg PE/kg/min or 150mg PE/ min, whichever is slower. An adult loading dose for a 60kg individual would deliver a total Captisol dose of 2400mg at a rate of 300mg/min. The applicant has not provided adequate support for the safety of this Captisol total dose or infusion rate based on reference to the Captisol DMF 14364, the published literature, or the bioequivalence studies. Adequate clinical support for the pediatric age range is not present in the DMF or applicant literature search.

[1] Guidance for Industry, Applications Covered by Section 505(b)(2), Draft Guidance 1999

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Status epilepticus is a life-threatening condition • Time based threat to neuronal survival • Metabolic, respiratory and hemodynamic complications accrue with increased duration of the status epilepticus episode	Early effective treatment of status epilepticus reduces the threat of immediate medical complications and long-term sequelae.
Current Treatment Options	• Cerebyx (fosphenytoin) - Requires refrigeration	Cerebyx (fosphenytoin) is not immediately available for emergency use by first responders.
Benefit	• Captisol-enhanced fosphenytoin may be stored at room temperature.	Captisol-enhanced fosphenytoin would be immediately available for the emergency treatment of status epilepticus by first responders.
Risk and Risk Management	• Cerebyx risks have been characterized since market approval in 1996 • Renal toxicity might occur with high exposure to the excipient Captisol in Captisol-enhanced fosphenytoin.	There is insufficient safety data to support the administration rate and total dose of the excipient Captisol and to rule out a nephrotoxic effect of captisol-enhanced fosphenytoin).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	**Patient experience data was not submitted as part of this application.**	

2. Therapeutic Context

2.1. Analysis of Condition

There is no change in the indication for this product from the listed drug CEREBYX. This product

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does not change the landscape of therapeutic options for the conditions indicated; therefore, an analysis of condition is not presented.

2.2. Analysis of Current Treatment Options

See response to section 2.1 above.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The listed drug, CEREBYX was approved in 1996. Examination of the most recent Annual Report of October 2, 2018 reveals no new significant clinical information.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-IND 9/7/2006 (applicant-CyDex)

Clinical / Clinical Pharmacology issues: It was noted that Captisol is an area of ongoing concern and that clinical studies should adequately monitor for potential nephrotoxicity. A panel of analytes from 24 hour urine collections was recommended. These should be collected immediately prior to IV administration, at the end of IV administration, at least 14 days after the last IV administration.

Design of the bioequivalence studies was considered. Out of concern for the safety of the normal adult volunteers in the intravenous study (A98), the applicant proposed decreasing the infusion rate or dose. The Agency agreed to consider an IV study at 150 mgPE/min and a 10mgPE/kg dose measuring free and total phenytoin and basing bioequivalence calculations on free phenytoin, noting that, in the intramuscular study, free phenytoin is not critical because rate is not a factor. the relevant PK parameters and BE comparisons should be provided for both total and free phenytoin for the IV route.

Pre-NDA 9/11/2008 (applicant- CyDex)

Clinical / Clinical Pharmacology issues: the applicant queried whether a safety report in needed in the NDA submission because the active ingredient, dosage form and route of administration is the same as forthe currently marketed listed drug (for which numerous generic ANDA have also been approved). The Agency agreed that a safety report for the fosphenytoin moiety would not be required but safety data from all clinical trials using the test formulation should be included. Moreover, the NDA submission should include a discussion of the potential toxicity of Captisol (including renal) in patients based on the overall daily exposure and rate of

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administration.

There was discussion on the approach to the concern about Captisol renal toxicity based on the preclinical finding of vacuoles in the renal tubules observed in the 14-day intravenous range-finding studies of Captisol in rat and dog. The Agency asked the applicant to consider both the total exposure and rate of exposure to Captisol from Captisol–enabled Fosphenytoin.

The applicant requested a waiver for pediatric studies under PREA. The Agency noted that status epilepticus has a significant incidence in the pediatric population and, since the extent of future pediatric use of Captisol enabled fosphenytoin is uncertain, a deferral rather than a waiver of the PREA- required pediatric studies is appropriate.

Type C, WRO 6/3/2016 (Sponsor-Sedor)

A discussion of efficacy studies concluded that no efficacy study is required if there is an adequate bridge to the reference drug fosphenytoin. If there is an adequate bridge, it is possible to rely in part on the safety of fosphenytoin but the safety of the captisol-fosphenytoin is important. The discussion references relevant discussion from the PreNDA meeting of 9/21/08 noted above. In addition, it is noted that subject narratives must be included for deaths, SAEs and adverse events leading to discontinuation.

Requirements for pediatric study were also covered in this meeting. The applicant was informed that the proposed 505(b)(2) application for Captisol-fosphenytoin does not trigger PREA so a pediatric study deferral and an iPSP is unnecessary. However, if there are any changes to the development plans that would cause the application to trigger PREA, then submission of a pediatric study plan, including a proposed waiver and/or deferral request would be required.

The applicant was advised that a proposed pediatric study request, pursuant to a Written Request under the Best Pharmaceuticals for Children Act (BPCA) could be submitted.

Pre-NDA 7/6/2017

The path of proprietary rights was covered in the background statement. CyDex Pharmaceuticals originally filed IND 74871 on September 24, 2007. Ligand Pharmaceuticals acquired CyDex on January 26, 2011. Subsequently, Sedor acquired the rights to license CE-Fosphenytoin on December 7, 2015.

The nonclinical issue of the Captisol excipient was considered. The Agency indicated that (in reference to other products):

- You may not rely on information from the Summary Basis of Approval (SBA) or FDA

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reviewers' public summaries to justify a safe level of an impurity/excipient; however, you may rely on labeling of a listed drug if that labeling indicates the level of the impurity/excipient.

- You may be able to rely on identified published literature about an impurity/excipient to support the safe use of a proposed level of an impurity/excipient. If the published literature describes a specific listed drug, you should provide an appropriate patent statement with respect to any relevant patents that claim the listed drug.

The format and content of clinical safety data was discussed. The discussion reinforced issues the Agency had presented in early meetings including the following:

- We further note that, in response to our requests in the Meeting Minutes of June 3, 2016, you plan to discuss the potential toxicity of sulfobutyl ether beta-cyclodextrin (Captisol) based on the overall daily exposure, C_{max}, and rate of administration of CE-fosphenytoin that you propose in draft labeling, making comparisons to (and considering the safety data from) both approved Captisol-containing products and also any other Captisol-containing products that you may have studied. Appropriate comparisons with the NOAELs observed in nonclinical studies (rat and dog) should be made.

- We also note that you do not plan to provide patient narratives since no patient (while on study drug) died, had SAEs, had AEs of special interest leading to discontinuation, had pregnancies, etc. You will need to provide narratives for all patient deaths, serious adverse effects, and adverse effects leading to patient withdrawal from the study regardless of whether the patients were on study drug or Cerebyx at the time.

- Safety datasets must be provided in SAS.xpt V5 format (not in Excel as requested by the applicant).

The applicant was also informed that the Pregnancy and Lactation Labeling Rule (PLLR) for fosphenytoin must be updated from 3/1/17 if new information becomes available. In addition, for the sulfobutyl ether beta-cyclodextrin component (Captisol), the applicant was told to request any information pertaining to PLLR content from its partner, Ligand Pharmaceuticals, Inc., and to provide a review and summary of that and any information in the available published literature.

The applicant was told that there should also be appropriate language regarding precautions for the administration of a drug with a Captisol component added to all the relevant sections of its proposed CE-fosphenytoin labeling. The inclusion of any information regarding

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bioequivalence will be a matter of review. In general, comparative PK data, unless important for the safe and effective use of the drug, is not included in labeling.

3.3. Foreign Regulatory Actions and Marketing History

None identified in the submission

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

BE studies inspection request was sent to the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS). They determined that an inspection is not warranted at this time for the sites listed since they had already been recently evaluated.

4.2. Product Quality

The Office of Product Quality (OPQ) review team recommended that the Agency issue a Complete Response Letter because the application does not include adequate information to ensure that the applicant can consistently manufacture a product that is suitable for the proposed clinical indications.

4.3. Clinical Microbiology

Not Applicable

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewers have concluded that the nonclinical data in the current application and available in the Captisol Drug Master File (for which a letter of authorization was submitted) are adequate to support initiation of adult clinical studies of CE-fosphenytoin but cannot support approval without adequate clinical safety data. Additionally, the juvenile animal toxicology study of Captisol in the Drug Master File is inadequate by design to support initiation of clinical studies for pediatric patients less than 12 years of age.

4.5. Clinical Pharmacology

Clinical Pharmacology (OCP) reviewers found the data from the two pivotal BE studies to be adequate to support approval. These two BE studies compared Sesquient to Cerebyx: Study A98

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(after IV Administration) and Study247 (after IM Administration). Bioequivalence (in terms of plasma phenytoin levels) was demonstrated in both studies, establishing a clinical bridge for SESQUIENT versus Cerebyx.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Two studies were performed to demonstrate the pharmacokinetics, relative bioavailability, safety, and tolerability of CE-fosphenytoin IM injection (Study 247) and CE-fosphenytoin IV infusion (Study A98).

Study 20-247-SA (hereafter called Study 247) was an intramuscularly administered, single-dose, double-blind, randomized, two-treatment, two-period crossover study. A total of 52 subjects participated in the study and 50 subjects completed both study treatment periods. A 14-day washout period separated the treatment doses administered in Periods 1 and 2. Treatment A consisted of a single dose of 1000 mgPE of CE-fosphenytoin administered in 4×5 mL intramuscular (IM) injections. Treatment B consisted of a single dose of 1000 mgPE Cerebyx administered in 4×5 mL IM injections.

Each subject received the dose of the assigned fosphenytoin sodium injection administered intramuscularly into gluteal muscle masses. To achieve the total of 1000 mg PE/period, each subject received 4 x 5 mL injections at the designated site. A surgical marker was used to quadrant the area for site of the injections. Each injection was administered slowly over a 30 second interval. The distance between each injection site was at least 5 cm. The injection site was cleansed with an alcohol wipe just prior to injection and allowed to dry. Injections were administered using the Z-track method. Any leakage from the injection site was noted. Band-Aids were applied as needed. All subjects were dosed in the right gluteus muscle in period 1 and the left gluteus muscle in period 2.

Study 20-A98-AU (hereafter called Study A98) was an intravenously administered, single-dose, double-blind, randomized, two-treatment, two-period crossover study. A total of 38 subjects

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participated in the study and 34 subjects completed both study treatment periods. Treatment A consisted of a single intravenous (IV) infusion of 10 mg PE/kg at rate of 150 mg PE/minute CE-fosphenytoin followed by a 14-day washout period. Treatment B consisted of a single IV infusion of 10 mg PE/kg at rate of 150 mg PE/minute Cerebyx.

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Table 1 Table of Clinical Studies

Study No.	Study Design and Objective	Enrolled Population	Study Drug, Dose, and Frequency	Number of Completed Subjects	Treatment periods
20-A98-AU	A Double-Blind, Randomized, 2-Treatment, 2-Period Crossover Study Comparing the Pharmacokinetics of Captisol-Enabled Fosphenytoin Sodium with Cerebyx after IV Administration	Healthy volunteers; 19 M/19 F; 23-53 yr	**Treatment A**: Test Formulation CE-fosphenytoin (Lot # 2108-102) (50 mg PE/mL) Dose = 1 × 10 mg PE/kg intravenous infusion at rate of 150 mg PE per minute 14 day washout period **Treatment B**: Reference product Cerebyx (50 mg PE/mL) Dose = 1 × 10 mg PE/kg IV infusion at rate of 150 mg PE per minute	34	Subjects were randomized to 1 of 2 treatment sequences: Sequence 1 (CE-fosphenytoin and Cerebyx) or Sequence 2 (Cerebyx and CE-fosphenytoin), with the periods separated by a 14-day washout period
20-247-SA	A Double-Blind, Randomized, 2-Treatment, 2-Period Crossover Study Comparing the Pharmacokinetics of Captisol-Enabled Fosphenytoin Sodium with Cerebyx Administered Via IM Injection in Normal Healthy Volunteers	Healthy volunteers; 26 M/26 F; 18-55 yr	**Treatment A**: Test Formulation CE-fosphenytoin (Lot #2108-102) 1000 mg PE (4 x 5 mL IM injections) 14 day washout period **Treatment B:** Reference product Cerebyx 1000 mg PE (4 x 5 mL IM injections)	50	Subjects were randomized to 1 of 2 treatment sequences: Sequence 1 (CE-fosphenytoin and Cerebyx) or Sequence 2 (Cerebyx and CE-fosphenytoin), with the periods separated by a 14-day washout period

5.2. Review Strategy

The reader is referred to the OCP (Clinical Pharmacology) review for assessment of the validity and accuracy of the studies that provide the clinical bridge from the proposed product to the LD Cerebyx (as noted in section 6 also). Safety assessment as described in section 7.1.

6. Review of Relevant Individual Trials Used to Support Efficacy

No clinical efficacy studies are submitted with this application. This new drug application (NDA) utilizes the 505(b)(2) regulatory pathway for its proposed Captisol – Fosphenytoin Sodium Injection product. The applicant proposes to rely on the Agency's findings of safety and efficacy for the fosphenytoin sodium reference listed drug (LD) CEREBYX® with bioequivalence studies of the intramuscular and intravenous administration routes as a clinical bridge to the LD.

The applicant is seeking indications identical to those listed in the CEREBYX labeling as stated below:

- CE-Fosphenytoin is indicated for the treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery.
- CE-Fosphenytoin can also be substituted, as short-term use, for oral phenytoin.
- CE-Fosphenytoin should be used only when oral phenytoin administration is not possible.
- Age boundaries for the indication are identified in the dosage and administration Sections 2.3 and 2.4 of the labeling where there is an entry for "Pediatric Dosing From Birth to < 17 Years of Age" In these entries, instruction is provided for loading dose and the non-emergent loading dose of the captisol-fosphenytoin product.

In response to question 4a of a Type C guidance meeting (WRO), written response June 3, 2016, the Agency indicated: "The BE studies appear to be adequate for a 505(b)(2) NDA submission. However, the acceptance of the results of these studies will be a review issue." The bioequivalence acceptability is examined in the Clinical Pharmacology review and the reader is referred to that document.

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Office of Clinical Pharmacology, Review of Bioequivalence, Core Entries

"The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 210864 and finds it acceptable from an OCP perspective."

"The clinical program included two pivotal bioequivalence (BE) studies to compare CE-fosphenytoin to Cerebyx: Study 20-A98-AU (CE-Fosphenytoin Versus Cerebyx® After IV Administration) and Study 20-247-SA (CE-Fosphenytoin Versus Cerebyx® After IM Administration). Bioequivalence (in terms of plasma phenytoin levels) was demonstrated in both studies, establishing clinical bridge for CEFosphenytoin versus Cerebyx."

"The demonstration of bioequivalence for CE-Fosphenytoin versus Cerebyx has been determined on the basis of bioequivalent plasma phenytoin levels; therefore, pharmacokinetic bridge for CEFosphenytoin versus Cerebyx has been established."

Sponsor's Conclusion on the Results of Studies A98 and 247 for the Support of Bioequivalence

Study 247

Table 2 Study 247, Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phenytoin in Plasma (from applicant summary of clin-pharm, page 12, Table 7)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA CV%
	Test	Ref	(Test/Ref)	Lower	Upper		
ln(C_{max})	19652	19942	98.6	97.1	100.1	1	4.53
ln(AUC_{last})	608220	620379	98	94.4	101.8	1	11.53
ln(AUC_{inf})	ND	ND	ND	ND	ND	ND	ND

a Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
c 90% Confidence Interval
ND: Not Determined (Extrapolated AUC_{inf} >20%)

Conclusions

• The geometric mean ratio (GMR) and 90% confidence intervals for ln(Cmax) and ln(AUC_{last}) were within the accepted 80% to 125% limits for total levels of phenytoin in plasma.
• Based on these results, the test formulation, CE-fosphenytoin is considered bioequivalent to the reference listed drug product (RLD) Cerebyx® following IM administration.

Study A98

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Table 3 Study A98, Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Free Phenytoin in Plasma Ultrafiltrate (from applicant summary of clin-pharm, page 9, Table 5)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA CV%
	Test	Ref	(Test/Ref)	Lower	Upper		
ln(C_{max})	1380	1312	105.1	100	110.5	1	12.13
ln(AUC_{last})	24120	22655	106.5	101.9	111.3	1	10.73
ln(AUC_{inf})	ND	ND	ND	ND	ND	ND	ND

[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
ND: Not Determined (Extrapolated AUC_{inf} >20%)

Conclusions

• The geometric mean ratio (GMR) and 90% confidence intervals for ln(Cmax) and ln(AUC_{last}) were within the accepted 80% to 125% limits for total and free levels of phenytoin in plasma and plasma ultrafiltrate respectively.
• Based on these results, the test formulation, CE-fosphenytoin is considered bioequivalent to the reference listed drug product (RLD) Cerebyx® following IV administration.

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7. Review of Safety

7.1. Safety Review Approach

All subject level adverse events will be examined for pooled studies A98 and 247 to assess the frequency of SAE's and discontinuations. Study 247 adverse events are not individually analyzed because priority is given to the IV administration where concern for events related to early T_{max} may be expected. There were no deaths in the studies. The mean change from baseline to test and reference product infusion will be examined using the SDTM, lbs.xpt datasets of each study. The applicant did not evaluate any mean changes. These datasets will also be evaluated for outliers in core laboratory parameters (identified in section 7.4.6). In the category of vital signs, systolic blood pressure will be evaluated for mean change from baseline to post infusion of both test and reference product. An outlier screen will be performed by identifying the minimum result captured from each group mean study period and sequence. If a marked outlier is identified the group will be examined for additional outlier and all values of individual outlier patients will be examined to determine the significance of the outlier finding. Only minimum outliers will be captured because the low side of systolic blood pressure change is of greater priority due to the know hypotensive effect of phenytoin.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

The safety database for this application is provided by two bioequivalence studies. These studies examine the PK properties of the captisol-fosphenytoin product (test product) compared to the listed drug CEREBYX. There are two studies, one to compare the IM pharmacokinetics (study 247) of the test product and listed drug and one to compare IV pharmacokinetics (study A98). These were both Randomized, Double- Blind, 2-Treatment, 2-Period Crossover Studies in healthy volunteers where each subject received a single dose of test product and reference product where the order was dependent on treatment sequence assignment. There are 85 subjects in the total safety population with 51 subjects in study 247 and 34 subjects in study A98. This represents 94 single exposures to test product.

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7.2.2. Relevant characteristics of the safety population:

Table 4 Demographics Characteristics of Studies A98 and 247*

Demographic Parameters	Bioequivalence Studies		
	Study A98 IV formulation (N=34) n (%)	Study 247 IM formulation (N= 51) n (%)	Total (N=85) n (%)
Sex			
Male	16 (47)	25 (49)	41 (48.2)
Female	18 (53)	26 (51)	44 (51.8)
Age			
Mean years (SD)	35 (9.2)	31 (9.6)	
Median (years)	32.5	29	
Min, max (years)	23,53	18, 53	
Race			
White	21 (61.8)	38 (74.5)	59 (69.4)
Black or African American	9 (26.5)	10 (19.6)	19 (22.4)
Asian	0	1 (2)	1 (1.2)
American Indian or Alaska Native	2 (5.9)	2 (3.9)	4 (4.7)
Native Hawaiian or Other Pacific Islander	0	0	0
Other[1]	2 (5.9)	0	2 (2.4)
Ethnicity			
Hispanic or Latino	11 (32.4)	27 (53)	38 (44.7)
Not Hispanic or Latino	23 (67.6)	24 (47)	47 (55.3)
Region			
United States	34 (100)	51 (100)	85 (100)
[1] **No entry for race**			
*derived from individual study ADSL, ADaM datasets			

Reviewer Comment: the demographic composition of the bioequivalence studies appears acceptable for phase 1 healthy volunteer studies.

7.2.3. Adequacy of the Safety Database:

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

None

7.3.2. Categorization of Adverse Events

The total preferred term adverse event entries were 502 (studies A98 and 247). Inspection of this small number of events allowed examination for splitting of related terms.

SOC (system organ class) entries were not provided in the adverse event datasets.

7.3.3. Routine Clinical Tests

Deficits encountered in the safety database were an absence of ECG interpretation. Only entries of normal or abnormal were present. There was 1 preferred term entry of "palpitation" in the adverse event dataset.

Overall, the safety data was adequate to assess for safety signals of concern in these single dose bioequivalence studies.

7.4. Safety Results

7.4.1. Deaths

There were no deaths in the bioequivalence studies.

7.4.2. Serious Adverse Events

There were no serious adverse events in subjects following test product treatment. There was a single serious adverse event in subject (b) (6) related to the reference product CEREBYX. This subject had a dose of CEREBYX exceeding the specified protocol dose. The subject experienced lightheadedness. Subject (b) (6) had a weight of 92 kg and received 1500 PE of reference product, a dose within the boundaries of an adult loading dose of 10 to 20mg PE/kg.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Six subjects from the combined safety flag datasets of study 247 and A98 discontinued the study due to adverse events. Five of these subjects discontinued during the reference (Cerebyx) treatment interval of the study. There is divergent information concerning the withdrawal of subject (b) (6) from study 247. In the summary of clinical safety page 22, Table 6 this subject is included as discontinued due to adverse event, while on page 23, Table 7 the subject is not included as a withdrawal due to adverse event and is entered as a withdrawal of consent. However, this subject did receive test treatment and discontinuation is the same day. The ADAE.xpt dataset identifies 5, non-serious adverse events for this subject on the day of test product treatment. These events include the preferred terms "dizziness", "nausea", "paresthesias lips", "pruritis-hand", and "somnolence", although a discontinuation flag is not entered for any of the events.

Reviewer comment: it is possible that consent withdrawal of subject (b) (6) was due to one of the adverse events experienced following treatment with test product. The adverse event preferred terms "dizziness", "nausea" and "somnolence" were among the most frequent events

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in both the test and reference groups while only two test treatment subjects experienced "paresthesias lips" and subject (b) (6) had the only preferred term entry for "pruritis-hand".

7.4.4. Significant Adverse Events

Adverse events were consistent with the labeling of the listed drug Cerebyx.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Safety Flag set

The safety flag dataset does not include subjects (b) (6), and (b) (6) from study A98 and subject (b) (6) from study 247 because an adverse event resulting in study discontinuation occurred during reference drug treatment in period 1 allowing no comparison between test product and reference product. Subject (b) (6) in study 247 was discontinued from study but had adverse events in period 1 where test drug product was scheduled during period 1. Therefore, this patient remains in the safety datasets examined in this section.

The ADECOD (dictionary derived) variable was examined. Event terms compared to MedDRA version 21.1. Many of the terms were not in the 21.1 version format. There were 133 preferred terms in the study A98 and 247 ADaM ADAE datasets (pooled). These were examined and recoded by the reviewer to the updated term that mapped to MedDRA version 21.1. After mapping the applicant's original adverse event terms, of which some appeared to be verbatim terms, there were 71 adverse event preferred terms from the total study A98 and 247 pooled datasets. From among the safety flag patients, there were 9 entries from 9 patients with no preferred term present in the ADECOD variable. The adverse event pooled and individual study A98 datasets were used for the following adverse event analysis.

Analyses of the pooled studies A98 and 247 was performed as well an analysis of study A98 alone. Study A98 was the IV formulation bioequivalence study. This delivery (IV) is more likely to have adverse events related to shorter T_{max} and a small window of higher exposure than the IM injection route. Study A98 is thus examined for events related to these properties.

Studies A98 and 247 Pooled Adverse Events

Treatment emergent adverse events from the pooled IV and IM bioequivalence studies A98 and 247 are examined. A comparison of adverse event frequency between test (captisol-fosphenytoin) and reference product (fosphenytoin) is performed.

Adverse events with a frequency in more than 10% of the test treatment group were "dizziness", "paraesthesia", "pruritus", "headache", "somnolence", "ataxia", "nausea", and "hypoacusis". From within these 8 preferred terms there were two, "pruritus" and "ataxia",

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where the frequency of occurrence was greater in the test treatment than in the reference. The most notable difference within the frequency of "ataxia" which occurred in 16.5% of the test group and 9.4% of the reference treatment group, Table 5.

Table 5 Pooled Study 247 and A98, TEAE in greater than 1 unique subject, Test compared to Reference Treatment

Preferred Term	captisol - fosphenytoin (test)	fosphenytoin (reference)	% A (test)	%B (reference)	TREAT A> TREAT B
Dizziness	37	38	43.5	44.7	0
Paraesthesia	23	24	27.1	28.2	0
Pruritus	19	18	22.4	21.2	y
Headache	16	16	18.8	18.8	0
Somnolence	16	19	18.8	22.4	0
Ataxia	14	8	16.5	9.4	y
Nausea	10	15	11.8	17.6	0
Hypoacusis	9	13	10.6	15.3	0
Paraesthesia oral	6	5	7.1	5.9	y
Tinnitus	6	8	7.1	9.4	0
Dysgeusia	5	7	5.9	8.2	0
Pruritus generalised	5	7	5.9	8.2	0
Dry Mouth	4	6	4.7	7.1	0
Injection Site Reaction	4	1	4.7	1.2	y
Visual impairment	4	0	4.7	0.0	y
Euphoric mood	3	4	3.5	4.7	0
Vomiting	3	2	3.5	2.4	y
Confusional state	2	3	2.4	3.5	0
Disorientation	2	2	2.4	2.4	0
Fatigue	2	0	2.4	0.0	y
Flushing	2	0	2.4	0.0	y
Injection site pruritus	2	2	2.4	2.4	0
Menstruation irregular	2	0	2.4	0.0	y
Oral dysaesthesia	2	0	2.4	0.0	y
Abdominal Pain	0	5	0.0	5.9	0
Rash	0	3	0.0	3.5	0
Feeling of relaxation	1	2	1.2	2.4	0
Hypotension	1	2	1.2	2.4	0
Tremor	1	2	1.2	2.4	0

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Study A98

Examination of the adverse events of study A98 reveals three preferred terms with a frequency greater than 10%. In one of these preferred terms, "dizziness", the frequency was higher in the test than in the reference formulation by a small margin. There were 15 preferred terms with an occurrence in more than one subject. From among all the 15 events with an occurrence in greater than 1 unique subject, the frequency was higher in test than reference treatment for three terms. The three terms with a frequency higher in the test formulation were "dizziness", "Visual impairment", and "fatigue". The frequency difference for dizziness was 23.5% in the test product compared to 21.2% in the reference product while the frequency of visual impairment in the test product was 3.5% compared to 0% in the reference product. However, there was a single occurrence (1.2%) of "blurred vision" in the reference product which is an event with overlap to the event of "visual impairment". The adverse event "fatigue" had a frequency of 2.4% in the test product compared to 0% in the reference.

Table 6 Study A98, TEAE in greater than 1 unique subject, Test compared to Reference Treatment

	Number of Subjects		**% of Subjects**		
PREFERRED TERM	**captisol-fosphenytoin (test)**	**fosphenytoin (reference)**	**captisol-fosphenytoin (test)**	**fosphenytoin (reference)**	**TREAT A> TREAT B**
Paraesthesia	21	23	24.7	27.1	0
Dizziness	20	18	23.5	21.2	Y
Pruritus	17	18	20.0	21.2	0
Somnolence	8	11	9.4	12.9	0
Headache	7	7	8.2	8.2	0
Dysgeusia	5	5	5.9	5.9	0
Dry Mouth	4	5	4.7	5.9	0
Hypoacusis	3	4	3.5	4.7	0
Visual impairment	3	0	3.5	0.0 (1 instance of "vison blurred")	Y
Confusional state	2	2	2.4	2.4	0
Disorientation	2	2	2.4	2.4	0
Fatigue	2	0	2.4	0.0	Y
Nausea	2	6	2.4	7.1	0
Tinnitus	2	2	2.4	2.4	0
Feeling of relaxation	1	2	1.2	2.4	0
Hypotension	1	2	1.2	2.4	0

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Reviewer Comment: Examination of the pooled adverse event table reveals the largest excess preferred term with higher frequency in test product than reference was “ataxia”. The contribution was predominantly from study 247. Among the remaining terms where frequency for test product exceeded that of the reference, the frequency difference did not exceed 5%. In study A98 there were three terms with an excess in the test product over the reference product, these were “dizziness”, “visual impairment” and “fatigue”. Overall, the test product does not reveal a notable difference in safety from the reference product based on examination of the treatment-emergent adverse effects.

7.4.6. Laboratory Findings

Study A98 (Test to Reference, IV administration), see Appendix 10.3 (A98 Study Report Reference Range Tables)

Concerning laboratory results for study A98, the applicant reports “The overall mean hematology, serum chemistry, and urinalysis results at screening, at check-in on Day -1 of both treatment periods, at check-in on Period 2 Day 14 (Period 1 Day 14 and Period 2 Day -1 were the same collection point), and at discharge of Period 2 were not summarized for Study A98.” The reviewer has performed examination of laboratory means and outliers derived from the SDTM, lbs.xpt dataset because study A98 offers the opportunity to examine the results of clinical laboratory studies obtained from intravenous administration of test and reference product. Test product is the fosphenytoin-captisol combination while reference product is fosphenytoin alone.

In this study subjects (b) (6) did not complete treatment period 2 infusion and received reference drug treatment in treatment period 1.

Mean Change in Clinical Chemistry Parameters

Blood Studies

Clinical Chemistry: Assessment of Group Mean Clinical Chemistry Parameter Before and Following Test Product (fosphenytoin- captisol) Infusion

The group mean values for chemistry parameters are examined. No clinically notable changes in mean values are identified for test products (captisol-fosphenytoin) for either study sequence AB or BA where A is the test product, see Table 7 and Table 8.

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Table 7 Clinical Chemistry, Group Mean Values with Percent Change for Test Product, Sequence AB (period 1), Pre-Infusion, Day 1 Post Infusion and Day 14 Post Infusion (n=19)

Clinical Chemistry Parameter	MEAN PRE-INFUSION	MEAN D14 POST INFUSION	GROUP MEAN DIFFERENCE, D 14 - PRE-INFUSION	MEAN % CHG
Albumin	4.22	4.16	-0.06	-1.42
Alkaline phosphatase	72.21	71.89	-0.32	-0.44
ALT (SGPT)	24.95	22.26	-2.69	-10.78
AST (SGOT)	20.84	18.63	-2.21	-10.60
Blood Urea Nitrogen	13.16	12.63	-0.53	-4.03
Chloride	103.58	103.58	0.00	0.00
Creatinine	0.84	0.86	0.02	2.38
Glucose	91.26	90.42	-0.84	-0.92
LDH	162.32	159.58	-2.74	-1.69
Potassium	4.66	4.57	-0.09	-1.93
Sodium	147.05	146.05	-1.00	-0.68
Total Bilirubin	0.52	0.47	-0.05	-9.62
Uric acid	4.46	4.29	-0.17	-3.81

Table 8 Clinical Chemistry, Group Mean Values with Percent Change for Test Product, Sequence BA (period 2), Pre-Infusion, Day 1 Post Infusion and Day 14 Post Infusion (n=15)

Clinical Chemistry Parameter	MEAN PRE-INFUSION	MEAN D14 POST INFUSION	GROUP MEAN DIFFERENCE, D 14 - PRE-INFUSION	MEAN % CHG
Albumin	4.08	4.15	0.07	1.63
Alkaline phosphatase	63.47	63.53	0.07	0.11
ALT (SGPT)	21.87	19.20	-2.67	-12.20
AST (SGOT)	19.93	18.20	-1.73	-8.70
Blood Urea Nitrogen	11.47	13.53	2.07	18.02
Chloride	104.20	105.47	1.27	1.22
Creatinine	0.91	0.90	-0.01	-0.74
Glucose	90.33	94.73	4.40	4.87
LDH	167.53	168.80	1.27	0.76
Potassium	4.41	4.67	0.26	5.89
Sodium	147.07	148.93	1.87	1.27
Total Bilirubin	0.41	0.41	0.00	0.00
Uric acid	4.56	4.60	0.04	0.88

Clinical Chemistry: Assessment of Group Mean Clinical Chemistry Parameters Before and Following Reference Product (fosphenytoin) Infusion

The group mean values for clinical chemistry parameters are examined. No clinically notable changes in mean values are identified for the reference product (fosphenytoin alone) for either study sequence AB or BA where B is the reference product, see Table 9 and Table 10.

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Table 9 Clinical Chemistry, Group Mean Values with Percent Change for Reference Product, Sequence AB (period 1), Pre-Infusion, Day 1 Post Infusion and Day 14 Post Infusion (n=19)

Clinical Chemistry Parameter	MEAN PRE-INFUSION	MEAN D14 POST INFUSION	GROUP MEAN DIFFERENCE, D 14 - PRE-INFUSION	MEAN % CHG
Albumin	4.08	4.15	0.07	1.63
Alkaline phosphatase	63.47	63.53	0.07	0.11
ALT (SGPT)	21.87	19.20	-2.67	-12.20
AST (SGOT)	19.93	18.20	-1.73	-8.70
Blood Urea Nitrogen	11.47	13.53	2.07	18.02
Chloride	104.20	105.47	1.27	1.22
Creatinine	0.91	0.90	-0.01	-0.74
Glucose	90.33	94.73	4.40	4.87
LDH	167.53	168.80	1.27	0.76
Potassium	4.41	4.67	0.26	5.89
Sodium	147.07	148.93	1.87	1.27
Total Bilirubin	0.41	0.41	0.00	0.00
Uric acid	4.56	4.60	0.04	0.88

Table 10 Clinical Chemistry, Group Mean Values with Percent Change for Reference Product, Sequence BA (period 2), Pre-Infusion, Day 1 Post Infusion and Day 14 Post Infusion (n=15)

CHTEST	MEAN PRE-INFUSION	MEAN D14 POST INFUSION	GROUP MEAN DIFFERENCE, D 14 - PRE-INFUSION	MEAN % CHG
Albumin	4.16	4.11	-0.05	-1.20192
Alkaline phosphatase	71.89	74.32	2.43	3.38
ALT (SGPT)	22.26	22.32	0.06	0.27
AST (SGOT)	18.63	19.95	1.32	7.09
Blood Urea Nitrogen	12.63	13.37	0.74	5.86
Chloride	103.58	104.95	1.37	1.32
Creatinine	0.86	0.86	0	0.00
Glucose	90.42	89.53	-0.89	-0.98
LDH	159.58	157.95	-1.63	-1.02
Potassium	4.57	4.58	0.01	0.22
Sodium	146.05	147.68	1.63	1.12
Total Bilirubin	0.47	0.37	-0.1	-21.28
Uric acid	4.29	4.37	0.08	1.86

Mean Change in Hematology Parameters

Hematology: Assessment of Group Mean Hematology Parameter Results Before and Following Test Product (fosphenytoin- captisol) Infusion

The group mean values for hematologic parameters are examined. No clinically notable changes in mean values are identified for test products (captisol-fosphenytoin) for either study sequence AB or BA where A is the test product, see Table 11 and Table 12.

Reference ID: 4406956

Table 11 Hematology, Group Mean Values with Percent Change for Test Product, Sequence AB (period 1), Pre-Infusion, Day 1 Post Infusion and Day 14 Post Infusion (n=19)

Hematologic parameter	Group mean pre-infusion	Group mean post infusion d1	Group mean d14	Day1 Post-inf.- Pre-infusion, Difference in Group Means	% Change of Group Means	Day 14 Post-inf.- Pre-infusion, Difference in Group Means	% Change of Group Means
Basophils (abs)	0.02	0.01	0.02	-0.01	-33.33	0.00	26.67
Eosinophils (abs)	0.28	0.21	0.23	-0.07	-25.93	-0.05	-19.07
Hematocrit	41.41	39.99	39.64	-1.42	-3.43	-1.77	-4.28
Hemoglobin	13.77	13.39	13.19	-0.38	-2.75	-0.59	-4.27
Lymphocytes (abs)	2.44	1.63	2.17	-0.81	-33.19	-0.28	-11.35
Monocytes (abs)	0.65	0.54	0.68	-0.11	-16.26	0.03	4.27
Neutrophils (abs)	3.91	4.05	4.21	0.15	3.77	0.30	7.80
Platelets	277.47	252.84	277.90	-24.63	-8.88	0.43	0.15
RBC Count	4.59	4.44	4.39	-0.15	-3.21	-0.20	-4.37
WBC Count	7.32	6.43	7.30	-0.88	-12.09	-0.02	-0.22

Table 12 Hematology, Group Mean Values with Percent Change for Test Product, Sequence BA (period 2), Pre-Infusion, Day 1 Post Infusion and Day 14 Post Infusion (n=15)

Hematologic parameter	Group mean pre-infusion	Group mean post infusion d1	Group mean d14	Day1 Post-inf.- Pre-infusion, Difference in Group Means	% Change of Group Means	Day 14 Post-inf.- Pre-infusion, Difference in Group Means	% Change of Group Means
Basophils (abs)	0.01	0.00	0.01	-0.01	-100.00	0.01	100.00
Eosinophils (abs)	0.20	0.13	0.21	-0.08	-37.50	0.01	3.33
Hematocrit	39.83	39.41	39.96	-0.43	-1.07	0.13	0.32
Hemoglobin	13.28	13.28	13.27	0.00	-0.04	-0.01	-0.10
Lymphocytes (abs)	2.27	1.46	2.32	-0.81	-35.67	0.05	2.05
Monocytes (abs)	0.56	0.49	0.60	-0.07	-11.83	0.04	7.14
Neutrophils (abs)	2.91	3.28	3.09	0.37	12.67	0.18	6.19
Platelets	279.80	256.25	279.93	-23.55	-8.42	0.13	0.05
RBC Count	4.48	4.46	4.48	-0.02	-0.46	0.00	0.06
WBC Count	5.94	7.45	6.25	1.51	25.42	0.31	5.27

Reviewer Comment (hematology parameters): Examination of reference product group mean changes were not performed to compare to test product means because no notable changes in test product means were seen.

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Outlier Examination

Hematologic Parameters - outliers

Outlier values are examined for the core hematologic parameters of hemoglobin, lymphocytes, neutrophils, platelets, and WBC counts.

No values for monocyte or lymphocyte counts were identified in test or reference product treatment.

Hemoglobin

One hemoglobin count is identified in reference product post infusion as 1.51g/dl; this is likely incompatible with life. All other entries for this subject are within normal limits. This represents a data entry error. Subject (b) (6) was found to have an out-of-reference range (OORR) value (10.9 g/dl) at discharge, 28 days after test product dose, as well at the end of period 2, day 14 which is 27 days after test product dose. All measurements more proximate in time to test product dose were within normal limits. Subject (b) (6) had an OORR low measurement beginning at the post-infusion interval of reference drug treatment. No measurements associated with the test product time sequence were OORR. Subject (b) (6) had an OORR low value of 11.1 g/dl at the pre-infusion measurement of test product in sequence BA with a further decline to 10.8 g/dL at the period 2 post-infusion value. This OORR low had normalized to 12.1 g/dl at discharge 13 days later. Subject (b) (6) had a single OORR low value of 11.3 g/dl at the post-infusion measurement of test product in sequence BA. This normalized by discharge 14 days later. Subject (b) (6) had two OORR range low values, one measured at 11.4 g/dl on the post infusion day. This declined a small amount further to 11.2 g/dl at the 14-day post infusion measurement but returned to normal range at the discharge measurement the following day. Subject (b) (6) had three OORR low values at test product post-infusion day 1 (period 1), pre-infusion of reference product in reference product and post infusion day 1 of reference product in period 2. The values were 11.4, 11.2, and 11.1 g/dl respectively. The hemoglobin had returned to normal range at discharge measurement. Subject (b) (6) had three OORR low values at test product post infusion day 1 (period 1), post-infusion of reference product on post-infusion day 1 and day 14 post-infusion in period 2. The values were 10.8, 10.7, and 10.6 g/dl respectively. The hemoglobin had returned to normal range at discharge measurement.

Subject (b) (6) had a single OORR low value of 10.8 g/dl after test product period 2 infusion on post-infusion day 1. This returned to reference range at 11.8 g/dl at the 14-day post-infusion measurement. Subject (b) (6) had a single OORR low value of 11.3 g/dl on post infusion day 1, period 2 after test product infusion. This returned to reference range at the next measurement 13 day later. Subject (b) (6) had three OORR low values at each period 2 measurement

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associated with test product. These values were 10.9, 11.4 and 11.4 g/dl. The hemoglobin returned to reference range at discharge.

Reviewer comment: None of the OORR low values were in a serious range, none were below 10.6 g/dl. Fifteen instances of OORR low values were identified after infusion in period 2 while 8 instances were identified in the interval after infusion in period 1. The OORR low values were more frequent in period two measurements regardless of association with test or reference product. This may be due to a decline in hemoglobin due to phlebotomy.

Lymphocytes

No lymphocyte counts are identified OORR low. Two instances from patient (b) (6) were in OORR high; these are not explored further.

Platelets

No subjects were identified with OORR low platelet values. There were 6 instances from 3 subjects with OORR high values.

Two subjects were identified with OORR high platelet values following reference product treatment. One subject had an OORR high value after test product treatment. This value was 417 x 103 / uL where the upper reference range limit is 415 x 103 / uL. This represent a minor elevation over normal; in addition, a discharge value obtained one day after the OORR high value was found to be within normal limits at 391 x 103 / uL.

WBC Count

There were 20 instances of OORR low WBC counts from 9 subjects. Subject (b) (6) had the lowest range of WBC count values, all are shown in Table 13. This subject had 3 adverse event entries in the ADAE dataset but none related to investigation (WBC count) or infection. The patient had a declining trend up to and including discharge value but there is no discussion of this patient in the A98 study report or the summary of clinical safety. Subject (b) (6) had a WBC count of 3.4 x 10^3 /uL in period 2, post infusion day 1. This normalizes to 5.3 x 10^3 /uL two weeks later but dips again to 3.8 x 10^3 /uL at discharge. The remaining 5 subjects had minor declines below the OORR low threshold. One of these subjects had an OORR low value at screening.

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Table 13 Subject (b) (6) WBC count, Study A98, Period 1 and 2

Subject (b) (6) WBC count				
SEQUENCE	**VISIT**	**Laboratory date**	**Measurement**	**WBC Count X 10^3 / uL**
BA	Screening	(b) (6)		6.5
BA	Period 1		Pre-Infusion	3.1
BA	Period 1		Post-Infusion	3.6
BA	Period 2		Pre-Infusion	3.5
BA	Period 2		Post-Infusion	3.0
BA	Period 2 Day 14			3.9
BA	Discharge			2.8

There were 12 instances of OORR high values from 4 subjects. The maximum value from among these measurements was 13.6 x 10^3 /uL. This value returned to reference range by discharge measurement 14 days later. No adverse event entry related to infection is present. The remaining OORR high values did not represent an elevation of clinical concern based on duration and value.

Neutrophils

There were 14 instances of OORR low neutrophil values from 5 subjects while there were 2 instances of OORR high neutrophil values from 2 subjects. From among OORR low values, the nadir was identified from subject (b) (6) at the critical threshold of 1.0 X 10^3 /uL at study discharge (day 28) with a baseline value of 5.0 X 10^3 /uL. The neutrophil values did not define a clear trend in relation to test or reference drug administration and, following the marked drop from baseline values, fluctuated around a mean of 1.6 X 10^3 /uL, see histogram for subject (b) (6) in Figure 1 . The remaining 4 subjects did not have a decline in neutrophil counts that reached a critical low threshold. On average the lowest value for all patients occurred on the day of discharge. The basis of this decline is likely due to the phenytoin treatment because no consistent trend was associated with test or reference product treatment.

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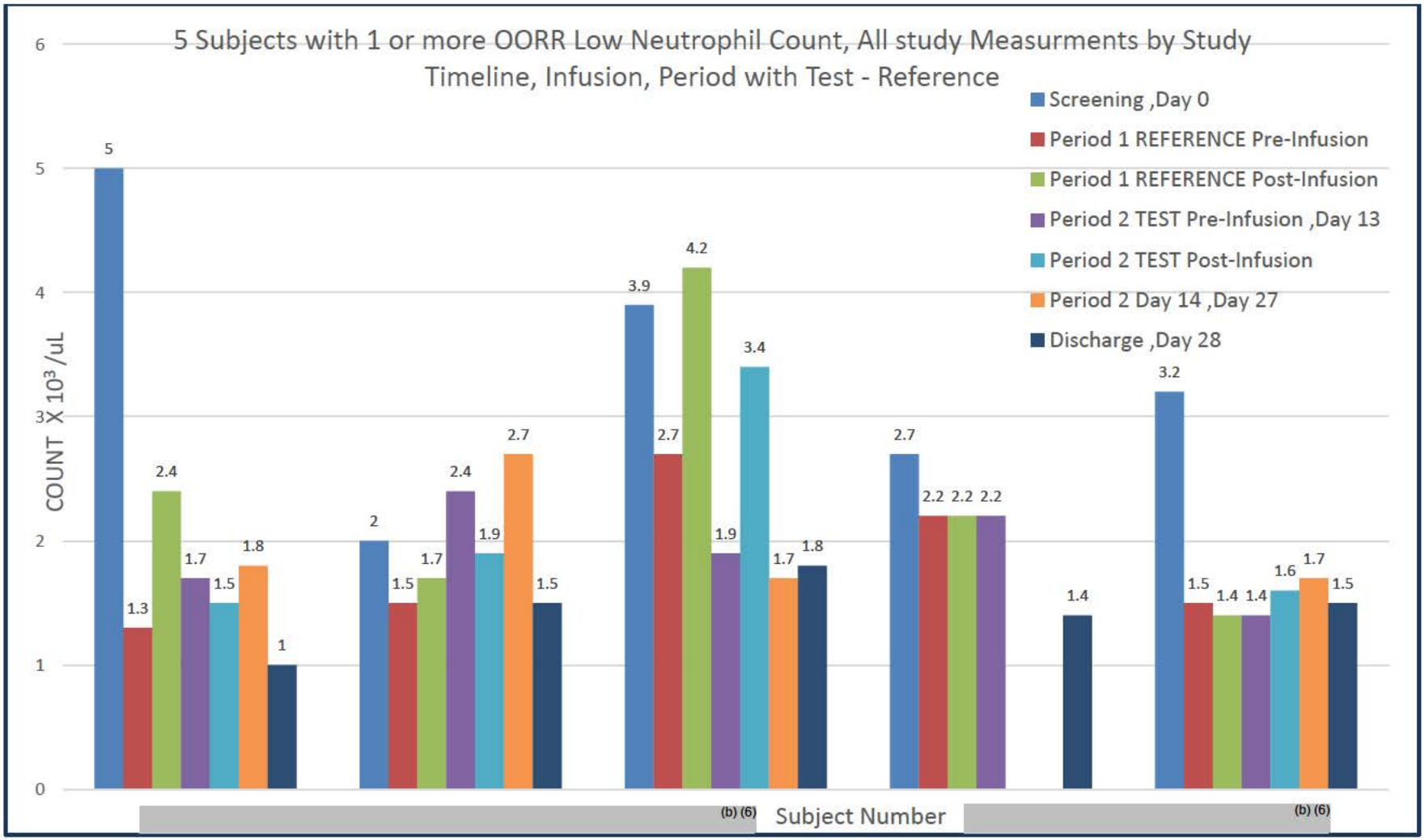
Figure 1 5 Subjects with 1 or more OORR Low Neutrophil Counts, All Study Measurements by Study Timeline, Infusion, Period with Test – Reference



Chemistry Parameters – Outliers

Core Parameters selected for outlier examination were ALT, BUN, Creatinine, Glucose, Potassium, Sodium and Total Bilirubin.

ALT

There were 3 subjects found to have any post treatment OORR high value. None exceeded twice the upper limit of normal, and the maximum observed was 1.4 x ULN. This value declined to just above normal limits 14 days later.

Total Bilirubin

No subject had a total bilirubin value greater than the upper limit of normal.

BUN

A single subject had an OORR high BUN value. This was observed 14 days following reference drug treatment in period 2. All other values for this patient were within normal limits and the discharge measurement was within normal limits.

Creatinine

No subject had a creatinine value greater than the upper limit of normal while two subjects had creatinine values that were at the upper limit of normal.

Glucose

No subjects had glucose values that were OORR high while there were 5 instances from 4 subjects with OORR low values. In three subjects the low value occurred at screening while in the remaining subject the screening value and pre-infusion period 2 value were both 76mg/dl.

Potassium

There were seven instances from 6 subjects with OORR high potassium value and none with OORR Low values. The OORR high values occurred at screening of two subjects. One subject had an elevated screening value and “period 2 day 14” value of 6.4meq/L and 6.2 meq/L respectively; therefore, these three subjects are not considered further.

The remaining three subjects with OORR high serum potassium values had one measurement each with a value above reference. These elevations are sporadic incidents without a consistent

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trend related to test or reference drug treatment (see Figure 2). These observations do not represent a safety signal for elevation of serum potassium.

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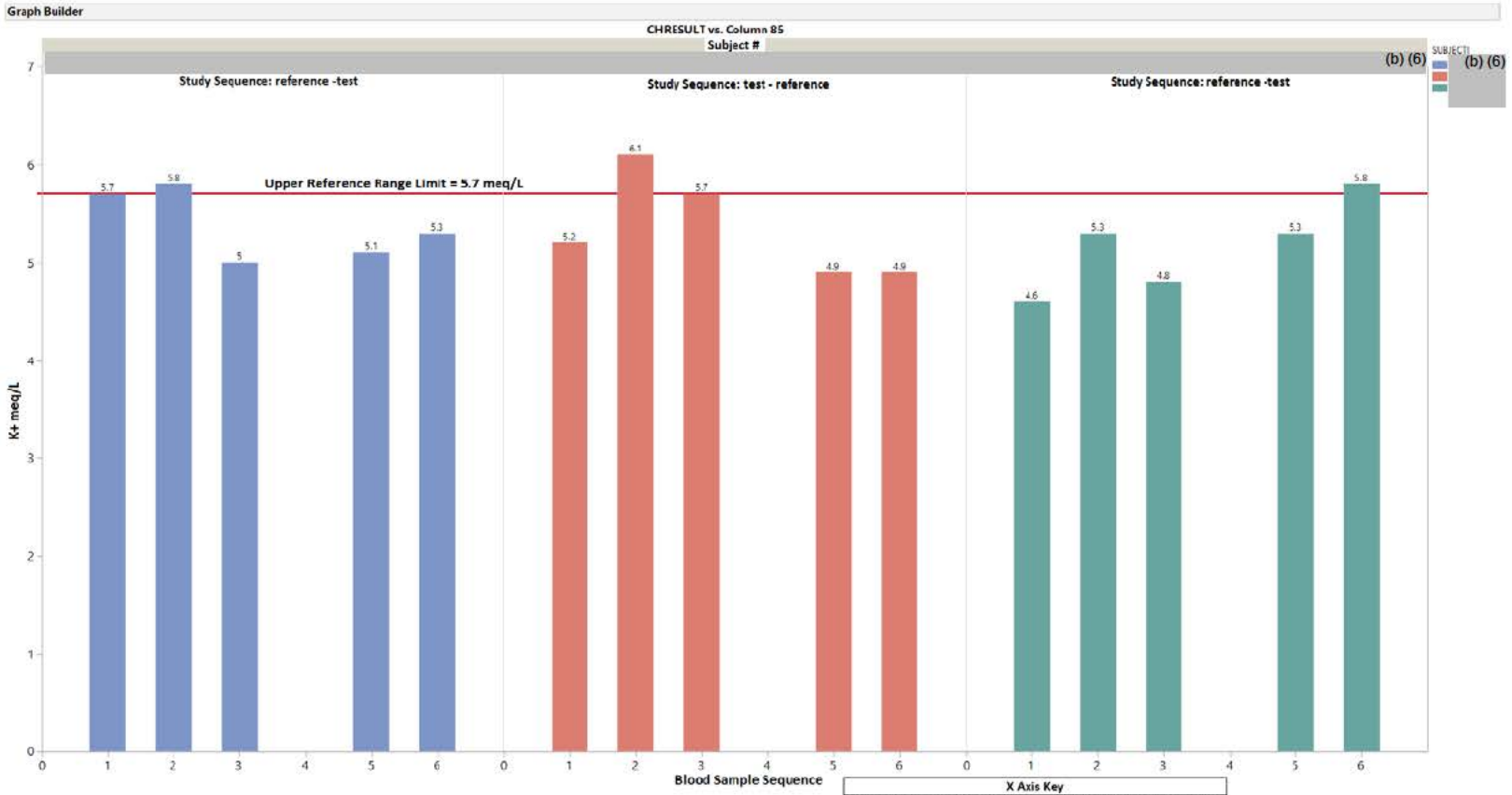
Figure 2 OORR High Potassium, 3 Subjects with Potassium Values by Study Timeline



X Axis Key			
Sample Sequence	Study Visit	Study Day	Infusion Status
1	Screening	0	
2	Period 1		Pre-Infusion
3	Period 2	13	Pre-Infusion
4	Period 2		Post-Infusion
5	Period 2 Day 14	27	
6	Discharge	28	

Sodium

There were 2 instances of OORR low sodium values from 1 subject. There were no OORR high sodium values (where upper reference range is 155meq/L). The OORR low measurements were identified from subject (b) (6) at period 1, pre-infusion and study discharge with values of 138meq/L and 139meq/L respectively. The period 1, pre-infusion value occurs prior to any drug treatment while the discharge value occurs 14 days following final infusion of reference drug. These are sporadically low values that bracket normal values during both test and reference drug periods and do not represent a safety signal.

The applicant's reference value for sodium is higher than the value presented in a major textbook table of clinical chemistry values of clinical importance where the reference range for sodium is 136–146 meq/L[2]. To explore the acceptability of the upper bound of serum sodium reference range in the A98 study report, all pre-drug treatment values are utilized to generate a mean, standard deviation and median. These pre-treatment samples include the screening and period 1, pre-infusion measurements. These laboratory study samples are available from 38 subjects. This yields a total of 76 data points. From this methodology the mean, median and standard deviation are found to be 147.5meq/L, 148meq/L and 2.5meq/L respectively. The mean is seen to be higher than the upper limit of normal of the reference range presented in a standard textbook of internal medicine[3]. Considering the results of this analysis, the applicant's upper limit of normal for sodium appears acceptable.

Urine Studies

Sponsor Comment on Urine Analytes (Module 2, 2.7.4, Summary of Clinical Safety, page 27): "Renal function was analyzed by monitoring urinary excretion of electrolytes and some low-molecular proteins to evaluate whether or not the Captisol in CE-fosphenytoin affects the kidney. Three 24-hour periods of urine were collected just prior to, immediately after, and 14 days following IV injection of the test drugs.

Results showed no changes in urinary excretion of β2-microglobulin, microalbumin, calcium, creatinine, phosphorus, and potassium among the three 24-hr periods. Statistically significant increases in urinary chloride and sodium were detected during the first day following

[2] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1130&sectionid=79722706. Accessed February 17, 2019

[3] Kratz A, Pesce MA, Basner RC, Einstein AJ. Laboratory Values of Clinical Importance. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e New York, NY: McGraw-Hill; 2014. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1130&sectionid=79722706. Accessed February 17, 2019

administration of test drugs; however, the magnitude of changes was small, and had little if any clinical significance. The increases in urinary chloride and sodium during the first 24 hours following drug administration could reflect the injection of normal saline solution that was used to dilute the drugs. When compared to the effects of the RLD (Cerebyx), those of CE-Fosphenytoin on urinary excretion of electrolytes and proteins were not different. "

Beta-2 Microglobulin, Urine (reviewer analysis)

Urine B2 Microglobulin is examined due to the observation of renal toxicity observed with use of cyclodextrins, see Appendix 10.4, β2-microglobulin as a Renal Biomarker and Section 7.5.1 Captisol. Captisol is a polysubstituted derivative of cyclodextrin; sulfobutylether-β-cyclodextrin sodium salt (SBECD), as an excipien (b) (4)

Examination of the urine Beta-2 Microglobulin laboratory dataset reveals 6 instances from 2 subjects with OORR high urine Beta-2 Microglobulin (based on the applicant reference range flag). One of these subjects had OORR high elevations at all measurements including pre-infusion period 1 (prior to any test or reference product treatment). The second subject, (b) (6) (b) (6) had a single elevation of urine Beta-2 Microglobulin 2 weeks after test product infusion, see Table 14. The subject had a value within reference range on the day following test product infusion while all pre and post infusion (includes Test and Reference) values were in normal range. This subject was also found to have a baseline OORR high flag with elevation of 24 hour urine creatinine value. Normal range is not provided by the applicant, so this baseline high value is compared to the mean and median value for all available pre-treatment measurements, see Table 15. This value is found to be 50% greater than the group mean baseline value. This raises the possibility that subject (b) (6) may have a pre-existing (baseline) renal lesion. The lack of temporal relationship between test drug infusion (2 week separation) and possible underlying nephropathy of subject (b) (6) reduces the likelihood of a causal relationship between beta 2 microglobulin increase and test product infusion.

To further explore the possible effect of the test product on the renal biomarker, beta 2 microglobulin, an analysis is performed to examine the change in group mean laboratory values from baseline to post treatment day 1 and baseline to post treatment day 14 for test and reference product infusion, see Figure 3 and Figure 4. Analysis of percent change of group mean, test product from baseline to day 1 post infusion reveals a decline in beta 2 microglobulin value. A decline is also seen for reference product in period 2 baseline to post infusion day 1. Examination of baseline to post infusion day 14 reveals a small increase of 23% over baseline. A similar increase of 27% is seen in reference product analysis. Percent change of group median values reveals a similar pattern.

Examination of sequence BA where reference product infusion occurs in period 1 and test

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product in period 2 is performed. This analysis reveals a 64% mean difference increase from baseline to post infusion day 1 for test product where reference product has only 2% increase. Analysis of baseline (period 2 pre-infusion) to post infusion day 14 reveals a group mean increase of 169% where the same analysis for reference product shows an increase of 33%. Examination of individual beta 2 microglobulin values reveals the percent increase seen for test product is driven by subject (b) (6) who has a very low baseline value of 4ug/L at period 2 pre-infusion. The mean and median beta 2 microglobulin values for period 2 pre-infusion are 77ug/L and 38ug/L respectively. Subject (b) (6) has a period 1 (reference product interval) pre-infusion value of 51ug/L while the period 2 day 1, post infusion and 14-day post infusion values are 39ug/L and 58ug/L respectively. Due to the baseline value of 4ug/L the post baseline values of 39ug/L and 58ug/L, of subject (b) (6), while below the group mean baseline value for period 2 (76ug/L), yield a change of 875% and 1350% respectively. These large values drive the percent difference of pre and post treatment group mean higher but do not represent an authentic elevation of beta 2 microglobulin in this test interval.

Figure 3 Urine Beta 2 Microglobulin, % Change of Group Means and Median by Collection Interval, Baseline to Post Infusion Day 1, Baseline to 14 Day Post Infusion, Sequence AB, (n= 19) Study A98

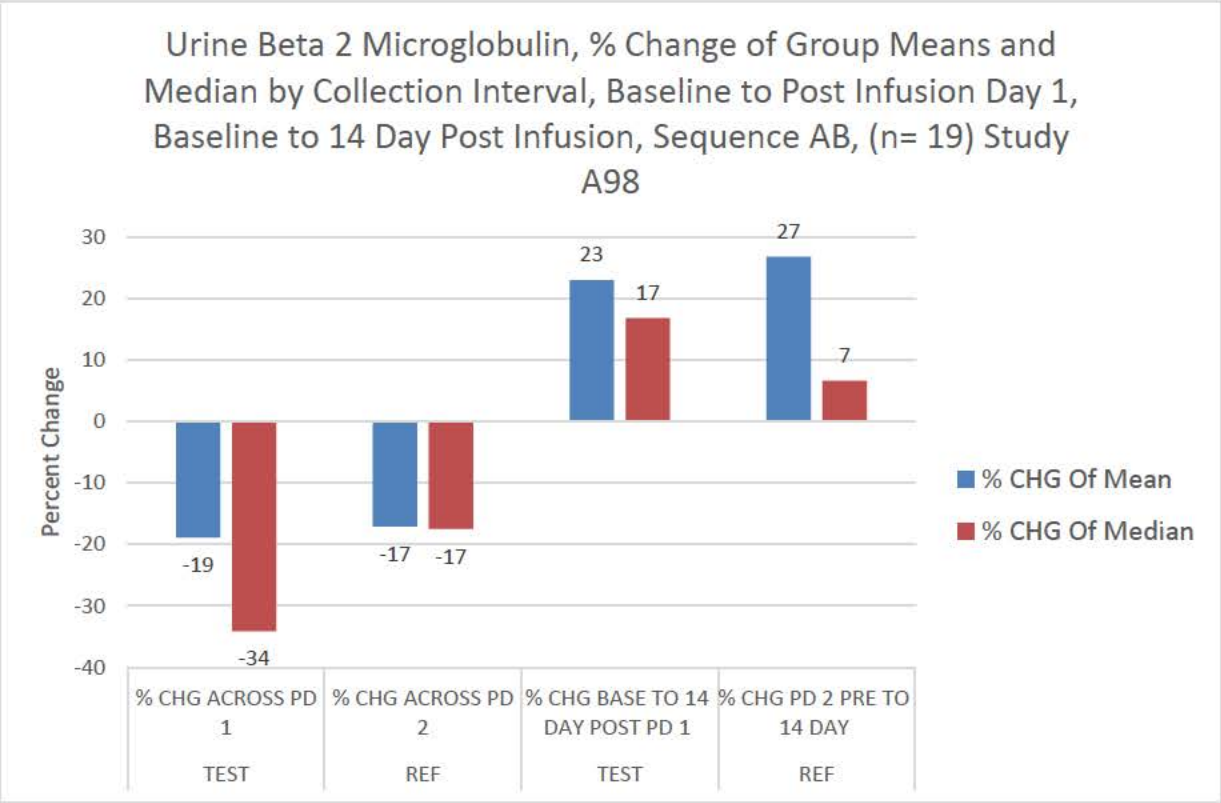
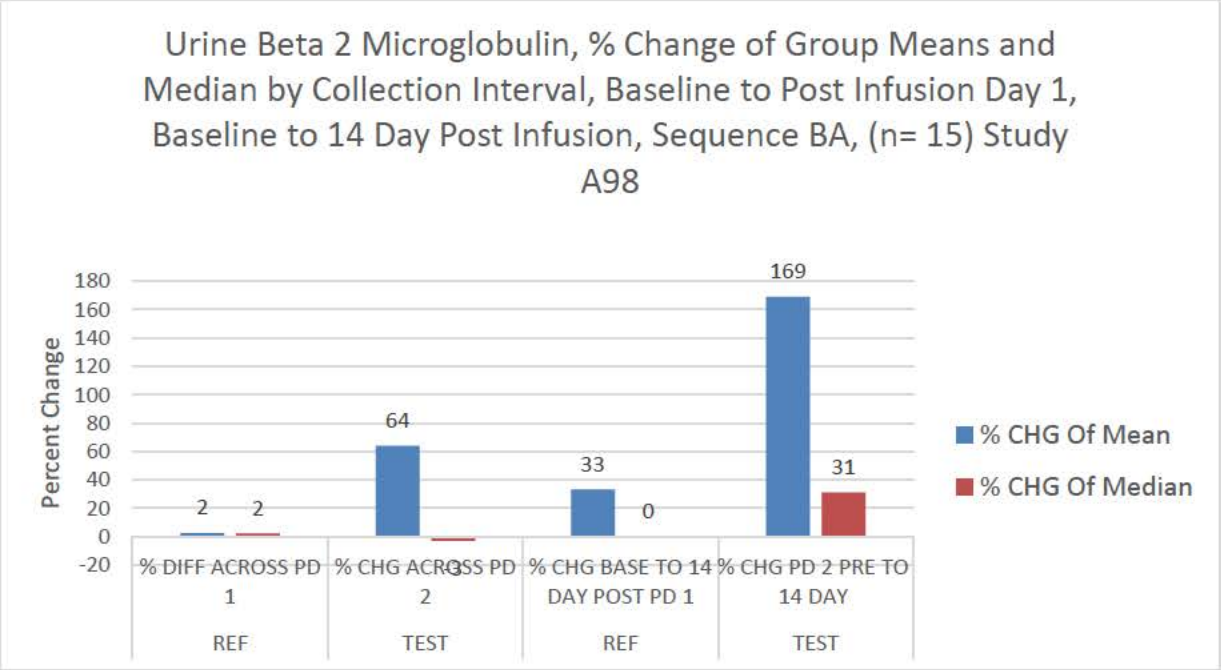


Figure 4 Urine Beta 2 Microglobulin, % Change of Group Means and Median by Collection Interval, Baseline to Post Infusion Day 1, Baseline to 14 Day Post Infusion, Sequence BA, (n= 15) Study A98



Reviewer comment: Examination of urine Beta-2 Microglobulin associated with intravenous infusion does not reveal evidence of a nephrotoxic effect of test product (captisol-fosphenytoin).

Table 14 Subject (b) (6) Urine Beta-2 Microglobulin, All Values

BASE vs POST-IINFUSION	VISIT	UCRSLT	UCFLAG
PRE-INFUSION	Period 1	290	
POST-INFUSION	Period 1	113	
PRE-INFUSION	Period 2	280	
POST-INFUSION	Period 2	125	
POST-INFUSION	Period 2 Day 14	861	High

Table 15 All Period 1, Pre-infusion (Pre-Treatment 24hr.) Urine Creatinine Values, Mean, Median, Standard Deviation (n=38)

Pre infusion pd 1 Mean(UCRSLT)	Median(UCRSLT)	Std Dev (UCRSLT)
1726.4	1646.25	563.4

Reviewer Comment, Study A98 Clinical Laboratory Results: examination of group mean change in clinical chemistry parameters from baseline to treatment reveals no notable change

associated with test or reference drug infusion. Examination of group mean change of hematology parameters reveals no notable change from baseline to test drug treatment. Outlier examination of hematology parameters reveals notable change in several WBC and neutrophil counts. These observations did not reveal a trend clearly related to test or reference product and there were no preferred term entries in the adverse events dataset related to infections. A myelosuppressive effect is identified in reference drug labeling (fosphenytoin) including leukopenia, granulocytopenia, agranulocytosis, and pancytopenia. The observed decline in WBC and neutrophil count are consistent with this labeled property of phenytoin. Examination of the selected chemistry parameters did not reveal notable outliers in the ALT, BUN, Creatinine, Glucose, Sodium and Total Bilirubin datasets. There were 3 subjects with elevated potassium values, however, these elevations are sporadic incidents without a consistent trend related to test or reference drug treatment. Examination of mean urine beta 2 microglobulin levels for test product in period 2 of sequence BA reveal a 169% increase in the group mean value at day 14 post infusion. This was found to be driven by a single patient with an anomalous low period 2 baseline but does not represent an authentic elevation of post treatment beta 2 microglobulin levels. Overall, no new safety signal is identified for the fosphenytoin-captisol product based on examination of study A98 laboratory parameters.

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Study 247 (test to reference IM administration)

Concerning laboratory results for study A98, the applicant reports "The overall mean hematology, serum chemistry, and urinalysis results at screening, at check-in on Day -1 of both treatment periods, and at discharge of Period 2 were not summarized for Study 247" The reviewer has performed an analysis of mean changes for chemistry and hematology values

Mean Change in Clinical Chemistry Parameters

Examination of test to reference product group mean change for clinical chemistry parameters from baseline to post treatment in period 2 reveals no notable changes from pre-injection to post injection within test or reference group or between test and reference groups. A single outlier, subject (b) (6) had an entry of 45 for post injection potassium value in the reference group. This value is not compatible with life and is excluded for the calculation of mean K+ value, see Table 16. There is no notable difference in baseline to post treatment group mean values in test or reference product.

Table 16 Study 247, Chemistry Parameters in Period 2, Test Means Pre to Post Injection Compared to Reference Mean Values Pre to Post Infusion with Percent Change Baseline (Pre) to Post Treatment

PERIOD 2	TEST MEANS			REFERENCE MEANS		
HEMATOLOGY PARAMETER	1 DAY PRE-INJECTION	DISCHARGE 2 DAYS POST-INJECTION	% CHG	1 DAY PRE-INJECTION	DISCHARGE 2 DAYS POST-INJECTION	% CHG
Albumin	4.3	4.3	-0.8	4.4	4.4	0.1
Alkaline phosphatase	75.0	76.3	1.7	82.4	83.0	0.7
ALT (SGPT)	24.0	22.0	-8.5	26.6	28.8	8.2
AST (SGOT)	21.7	20.5	-5.4	24.2	26.0	7.1
Blood Urea Nitrogen	12.8	12.9	0.9	12.8	13.4	4.5

PERIOD 2	TEST MEANS			REFERENCE MEANS		
HEMATOLOGY PARAMETER	1 DAY PRE-INJECTION	DISCHARGE 2 DAYS POST-INJECTION	% CHG	1 DAY PRE-INJECTION	DISCHARGE 2 DAYS POST-INJECTION	% CHG
Chloride	104.1	103.8	-0.4	103.8	103.1	-0.7
Creatinine	0.9	0.8	-5.3	0.9	0.9	3.2
Direct Bilirubin	0.0					
Glucose	88.9	87.7	-1.4	85.2	86.6	1.6
LDH	161.4	162.0	0.3	174.2	170.7	-2.0
Potassium	4.6	4.7	1.2	4.6	4.8	5.4
Sodium	147.3	147.3	0.0	147.9	146.9	-0.7
Total Bilirubin	0.5	0.4	-15.4	0.5	0.4	-21.9
Uric acid	4.3	4.2	-1.2	4.7	6.5	37.5

Mean Change in Hematology Parameters

Examination of test to reference product group mean change from baseline to post treatment in period 2 reveals no notable changes from pre-injection to post injection within test or reference group or between test and reference groups see Table 17. There is no notable difference in baseline to post treatment group mean values in test or reference product.

Table 17 Study 247, Hematology Parameters in Period 2, Test Means Pre to Post Injection Compared to Reference Mean Values Pre to Post Infusion with Percent Change Baseline (Pre) to Post Treatment

PERIOD 2	TEST MEANS			REFERENCE MEANS		
HEMATOLOGY PARAMETER	1 DAY PRE-INJECTION	DISCHARGE 2 DAYS POST-INJECTION	% CHG	1 DAY PRE-INJECTION	DISCHARGE 2 DAYS POST-INJECTION	% CHG
Basophils %	0.4	0.5	14.6	0.3	0.4	30.2
Basophils (abs)	0.0	0.0	-16.7	0.0	0.0	4.2
Eosinophils %	3.6	4.2	17.6	3.0	3.0	1.4
Eosinophils (abs)	0.2	0.3	30.3	0.1	0.1	40.0
Eosinophils (abs)	0.4	0.4	-9.5	0.2	0.2	-11.9
Hematocrit	40.5	41.3	2.1	41.5	42.5	2.5

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PERIOD 2	TEST MEANS			REFERENCE MEANS		
HEMATOLOGY PARAMETER	1 DAY PRE-INJECTION	DISCHARGE 2 DAYS POST-INJECTION	% CHG	1 DAY PRE-INJECTION	DISCHARGE 2 DAYS POST-INJECTION	% CHG
Hemoglobin	13.6	13.7	0.4	14.2	14.3	0.7
Lymphocytes %	31.2	34.0	8.8	32.5	34.5	6.3
Lymphocytes (abs)	2.2	2.2	-2.1	2.5	2.4	-2.4
Monocytes %	8.6	9.1	5.6	8.3	10.3	24.8
Monocytes (abs)	0.6	0.6	-2.5	0.6	0.7	9.4
Neutrophils %	56.2	52.4	-6.8	56.1	51.9	-7.5
Neutrophils (abs)	4.1	3.5	-15.3	4.4	3.7	-15.1
Platelets	279.7	270.6	-3.3	272.5	259.3	-4.8
RBC Count	4.7	4.6	-0.4	4.7	4.7	0.4
WBC Count	7.3	6.7	-9.1	7.7	7.1	-8.0

Reviewer Comment: Examination of means for hematology and clinical chemistry parameters reveals no notable change between baseline and post treatment values in period 2 from pre-injection to post-injection for test and reference products or between test and reference products.

Urine Beta 2 microglobulin

Mean values of pre and post treatment beta 2 microglobulin expressed as ug/mg creatinine/24hr from urine collection are examined for test product. There is a decline in mean value from baseline to post treatment day 1 for test product with a small group mean value increase of 0.2% at day 14 post test product injection. No notable increase of urine beta 2 microglobulin is associated with test product injection.

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Outlier Examination

Hepatic outliers (only OORR high considered)

There were 11 instances of elevated ALT from 5 subjects. The maximum ALT evaluation was 2.5 x ULN. In four of the five subjects the ALT elevation is observed in association with reference product treatment. In the remaining patient all ALT values from screening through discharge were elevated.

There were 11 instances of Total Bilirubin elevation from 6 subjects. The maximum elevation was 1.7 x ULN. In one subject the only elevation was at screening. In three subjects the elevation was observed in association with both reference and test treatment (period 1 and 2). In one subject the total bilirubin was elevated at screening but escalated in period one post treatment in the AB sequence and was thus associated with test product. In the remaining subject elevation of the same magnitude persisted from screening through both periods 1 and 2. There was no overlap of subjects with elevated ALT and Total bilirubin.

Renal Outliers (only OORR high considered)

There was a single patient with an OORR high creatinine value of 1.5mg/dl (1.07 x ULN) in the AB sequence associated with period 1. The Screening value was 1.2mq/dl while the value re-entered reference range in period two and at discharge. There were no subjects with OORR high values for blood urea nitrogen (BUN)

Hematology Outliers

A spot analysis of minimum outliers for period 2, test and reference products both at pre and post injection is performed. There were no notable minimums identified at post injection for either test or reference product.

Chemistry Outliers

A spot analysis of minimum outliers for period 2, test and reference products both at pre and post injection is performed. There were no notable minimums identified at post injection for either test or reference product.

Reviewer Comment: Period 2 examination of group mean change in values for hematology and clinical chemistry parameters between baseline and post injection of test product reveal no clinically significant change associated with test product treatment. When compared with the group mean changes in reference product there is no notable difference in the group mean changes in hematology and clinical chemistry parameters between the test and reference

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product injections. Examination of hepatic and renal outliers do not reveal evidence of a safety signal associated with test product. Examination of mean change in beta 2 microglobulin reveals no clinically meaningful change from baseline to post treatment values.

7.4.7. Vital Signs

STUDY A98 IV

The applicant reports hypotension in one subject ((b) (6)) in study A98. This event occurred associated with test product infusion at 12 minutes post infusion with a duration of approximately 3 hours. There were three addition adverse events of hypotension associated with reference product infusion that occurred at 11, 15 and 10 minutes post infusion. One of the three subjects in the reference product group discontinued due to the event of hypotension.

The group mean systolic and diastolic blood pressure values for test and reference product by study sequence are examined. There is a trend of decline in systolic and diastolic means after infusion that return toward baseline over the post infusion interval. There is no notable difference between the test and reference group mean values (see Appendix 10.5, Vital Signs, Group Mean Systolic Blood Pressure, Minimum Systolic & Diastolic Pressure by Group, Figure 9, and Figure 10).

The single minimum systolic and diastolic blood pressure values at each post infusion time interval are also examined by test and reference product and study sequence (AB-BA), see Appendix 10.5, Vital Signs, Group Mean Systolic Blood Pressure, Minimum Systolic & Diastolic Pressure by Group, Figure 11. The test product analysis reveals a minimum systolic blood pressure of 54mmHg in period 1 (subject (b) (6)) while the minimum systolic pressure in the period 1 reference product treatment is 77. In period 2 the minimum test product systolic blood pressure is 70mmHg (subject (b) (6)) while in the period 2 reference product the minimum systolic blood pressure is 82mmHg.

The observation of low minimum systolic blood pressure measurements associated with test product treatment prompted additional exploration of the occurrence of low post infusion systolic blood pressure. All systolic blood pressure measurements are sorted to identify any less than 80mmHg. There were 19 instances from 4 subjects with systolic pressure values less than 80mmHg. Fifteen of these instances, 79% of all low values, occurred following test product infusion while 4 instances, 21% of the low-pressure entries were following reference product infusion. Nine instances less than 80mmHg were from a single subject ((b) (6)) who had values less than 80mmHg following both test and reference product infusion.

There were 19 instances from 4 subjects with a systolic blood pressure entry less than 80mmHg. All but 1 of these instances occurred within the 1st hour post infusion the remaining

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instance occurred at 3 hours post infusion. One of the 4 subjects had a period 2 baseline (pre-infusion) value of 77mmHg. This leaves 3 subjects, 8%, with a post infusion systolic blood pressure less than 80mmgHg not present at pre-infusion.

Subject, (b) (6), had an additional 5 instances, following test product of post infusion, of systolic blood pressure less than 80mmHg, 4 occurred within the 1st hour and one at hour 3. This subject's profile of systolic blood pressure following reference product treatment was similar.

Examination of the reference product 1st hour post infusion dataset identifies 3 subjects that had an entry of systolic blood pressure less than 80mmHg (pre-infusion>80mmHg).

From among the remaining three subjects with normal pre-infusion (baseline) systolic blood pressure there were 10 instances of systolic blood pressure less than 80mmHg. These all occurred within the 1st hour post infusion. Examination of all instances of systolic pressure less than 80mmHg reveals that all but 1 occur within the 1st hour, while one instance as noted above had an instance at hour 3.

All systolic blood pressure measurements during hour 1 post infusion following test and reference product are examined. The mean and median systolic pressure from all values from <0 hr up to and including 1 hour for test product were 106mmHg and 107.5mmHg respectively. The mean and median systolic blood pressure values for the reference product in the same time interval were 109mmHg and 108mmHg respectively. This same analysis is performed for all post infusion systolic blood pressure measurements for test and reference products up to and including 2 hours. The mean post infusion systolic pressure associated with test and reference products were 107mmHg and 109mmHg respectively while the median systolic blood pressure is 108mmHg in both groups, see Table 18.

Table 18 Study A98, Mean and Median Systolic Blood Pressure from 0 to 1 hour and 0 to 2 hours following Test and Reference Product Infusion.

0 to 1hr			
TEST REF	Instance of blood pressure measurement	Mean	Median
REF	162	109	108
TEST	140	106	107.5
0 to 2hr			
REF	211	109	108
TEST	183	107	108

The distribution of pre-infusion (baseline) blood pressure values for both test and reference product sequences is examined to determine if low outlier post-infusion values may be

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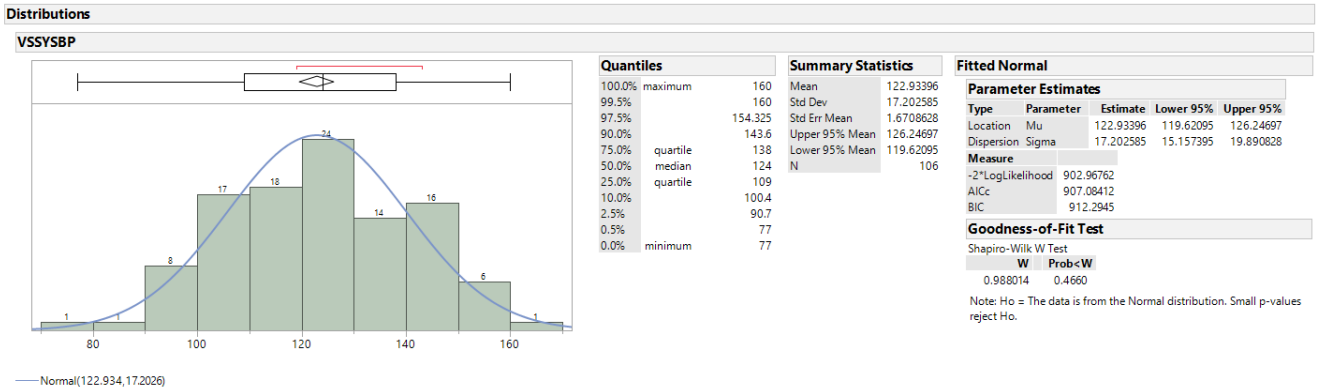
expected. The distribution of baseline systolic blood pressures approximates a normal distribution. A goodness of fit test indicates the distribution is close to normal in distribution, see Figure 5

Figure 5 Study A98 Distribution of all Pre-Infusion (baseline) Systolic Blood Pressure Values



From Figure 5 above there are 8 instances from 5 subjects with baseline systolic blood pressure less than 100mmHg. This near normal distribution of baseline systolic blood pressure values with a minimum of 77mmHg supports the potential for low post infusion outlier values based on hemodynamic characteristics of this population.

Reviewer Comment: There were 18 instances of post infusion systolic blood pressure with a value less than 80mmHg where most instances occurred following test product infusion. All these instances were derived from 4 subjects. One of the subjects has a baseline (pre-infusion) blood pressure of 77mmHg. When this subject is excluded, there were three remaining subjects. From among these subjects, an event of systolic pressure less than 80mmHg occurred following reference product infusion in one subject. One of the remaining two subjects had low systolic pressure values following both reference and test product infusion, although 6 of 7 instances were following test product. The remaining subject had two instances following test product infusion. Overall there were 3 subjects (8%) with pre-infusion systolic blood pressure >80mmHg with a post infusion test product systolic BP less than 80mmHg. In one of these subjects the baseline systolic pressure was 93mmHg. In the 1st hour post infusion of reference product, there were 3 (8%) subjects who had a systolic blood pressure measurement < 80mmHg. Although the low outliers found in the test product post infusion interval were lower than those observed for reference product, the proportion of subjects with a value <80mmHg was similar for both test and reference product.

Examination of group mean values revealed no notable difference in mean and median systolic blood pressure values of test and reference product in the 1 hour or 2-hour post infusion

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window. These observations do not indicate there is a differential post infusion effect on systolic blood pressure between test and reference products.

Study 247 (IM)

The applicant reports no findings of clinical significance in the vital signs examination of study 247.

The group mean systolic and diastolic blood pressure values for test and reference product by study sequence are examined. There is a trend of decline in systolic and diastolic means after infusion that return toward baseline over the post infusion interval. There is no notable difference between the test and reference group mean values see Appendix 10.5, Vital Signs, Group Mean Systolic Blood Pressure, Minimum Systolic & Diastolic Pressure by Group, Figure 12 and Figure 13. Examination of the group (test- reference) minimum systolic blood pressure values reveal a trend of decline in the first 2 hours of the post infusion interval but without the divergence in magnitude of values observe in test interval compared to reference that was seen in study A98 above, see Figure 14.

Examination of all systolic blood pressure entries from study 247 reveals 4 instances from 3 subjects where the systolic blood pressure is less than 80mmHg. In two of these subject where the low systolic pressure was following test product infusion, the pre-infusion blood pressure was <80mmHg. In the third subject the event of systolic pressure <80mmHg occurred following reference product infusion.

Reviewer Comment: Examination of systolic blood pressure in Study 247 reveals post infusion decline in systolic blood pressure but there is no differential signal for low systolic blood pressure between the test and reference product.

Overall Blood Pressure Summary: Both systolic and diastolic blood pressures are seen to decline in the post infusion interval for both products. The instances of low post infusion systolic blood pressure (with pre-infusion >80mmHg) in study A98 after test product had a frequency of 8% where no instances, with pre-infusion (baseline) value >80mmHg, of low systolic pressure in the test product post infusion interval were identified in study 247. Hypotension is an adverse effect identified in the labeling for Dilantin injection. Whether this effect is due to phenytoin or the injection vehicle is not elucidated. Cerebyx labeling identifies hypotension as a warning in Section 5.2 “Cardiovascular Risk Associated with Rapid Infusion” in addition, monitoring of blood pressure during Cerebyx infusion is recommended in section 2, dosing and administration. The recommendation is directed specifically at the treatment interval where maximal serum phenytoin concentrations occur. The phenytoin specific hypotensive effect is observed following intravenous infusion in study A98 with no conclusive differentiation of this effect between test and reference product infusion.

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7.4.8. Electrocardiograms (ECGs)

Study A98

No abnormal post infusion ECG entries are present in the study A98 ecg.xpt dataset.

Study 247

The applicant identifies two "conduction treatment related adverse effects in study 247. These occurred in the interval following reference product infusion. The ecg.xpt dataset was examined. There were three subjects with an entry for "abnormal" interpretation at discharge, 2 days following test product infusion. There is no further interpretation of these studies in the dataset.

7.4.9. QT

No QT study is performed. The captisol associated fosphenytoin is seeking reliance (via 505b2 pathway) on Cerebyx for safety of the API.

7.4.10. Immunogenicity

This is a small molecule moiety not expected to evoke antibody production

7.5. Analysis of Submission-Specific Safety Issues

7.5.1. Captisol

Due to relatively poor aqueous solubility of some active pharmaceutical ingredients, a cyclodextrin derivative has been utilized to allow for an intravenous delivery option. The parenteral formulation incorporates a polysubstituted derivative of cyclodextrin, sulfobutylether-b-cyclodextrin sodium salt (SBECD), as an excipient for solubilization. Some cyclodextrins, notably those occurring in nature that have not been further synthetically modified, have either been associated with drug associated hepatotoxicity or nephrotoxicity. Unmodified cyclodextrins, namely a- and b-cyclodextrins, are typically reabsorbed and concentrated in the renal tubule, interacting with and extracting cholesterol and other lipid membrane components from cellular structures. Reabsorption and concentration of both the relatively soluble parent cyclodextrins and the insoluble cyclodextrin/cholesterol complexes affect cellular integrity.[4]

[4] Luke DR, et. al. Review of the Basic and Clinical Pharmacology of Sulfobutylether-b-Cyclodextrin (SBECD). JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 99, NO. 8, AUGUST 2010. DOI 10.1002/jps.22109

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Captisol, SBECD (see Figure 6) is a second-generation cyclodextrin chemically-engineered not to accumulate in renal epithelial cells and thus avoid acute kidney injury. Despite limited evidence that SBECD has not been associated with renal impairment, restrictions in its use in patients with estimated creatinine clearances (Clcr) less than or equal to 50 mL/min have been documented.[5] There is potential for renal toxicity of SBECD based on nonclinical data. "SBECD appears to be well tolerated in humans, but in animal studies, vacuolation of epithelial cells of the urinary tract as well as an activation of macrophages in liver and lung was observed after repeated doses of SBECD. SBECD is a pharmacologically inert agent. The terminal half-life of SBECD in humans with normal renal function is 1.8 h"

Figure 6 Structural formula of sulfobutylether-b-cyclodextrin sodium salt (SBECD)[6]

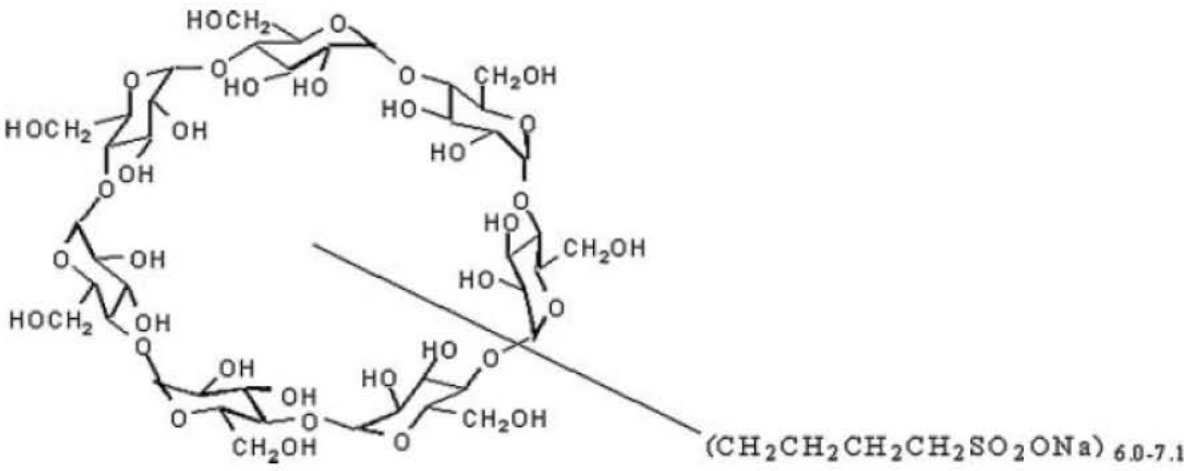

Figure 1. Structural formula of sulfobutylether-β-cyclodextrin sodium salt.

Bioequivalence to the listed drug was established for intravenous and intramuscular administration in studies A98 and 247 respectively. This establishes a bridge to rely on the findings for safety and efficacy of the fosphenytoin sodium listed drug CEREBYX®. The need for a 505b2 pathway is based on the change in formulation for the proposed drug that contains a different quantity of excipients than the listed drug.[7] This excipient, Captisol, is present in the proposed formulation in a 2:1 proportion (Captisol 2mg : fosphenytoin 1mgPE). The formulation will deliver the excipient, not present in the listed drug, at a rapid rate when administered for

[5] Lilly et al. BMC Infectious Diseases 2013, 13:14 Page 2 of 8
http://www.biomedcentral.com/1471-2334/13/14
[6] Luke DR, et. al. Review of the Basic and Clinical Pharmacology of Sulfobutylether-b-Cyclodextrin (SBECD). JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 99, NO. 8, AUGUST 2010. DOI 10.1002/jps.22109
[7] Guidance for Industry, Applications Covered by Section 505(b)(2), Draft Guidance 1999

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the indication of status epilepticus. Although the proportional delivery of Captisol per mg of API (fosphenytoin) is low in the proposed product compared to several other products that utilize this excipient, an adult loading dose of the proposed captisol-fosphenytoin product will deliver captisol at a rate of 300mg/min with a total dose of 2400mg in a 60kg patient.

An excipient with an exposure that is twice that of the active pharmaceutical ingredient must have appropriate safety support. The applicant references Captisol DMF 14364 (see Appendix 10.6 *Summary Table DMF 14364, Clinical Data Entry Content with Assessment of Relevance)* and published literature (see Appendix 10.7, *Summary Table of Sponsor Literature References, Clinical Data Content with Assessment of Relevance*) in their NDA submission. The safety data contained in this documentation is insufficient to support the safety of captisol for use with the listed drug.

In the history of this application, CyDex pharmaceutical performed the studies to assess IV and IM bioequivalence to the listed drug Cerebyx. These studies A98 and 247 respectively were performed in 2008. These studies were subsequently reissued to the current applicant, Sedor Pharmaceuticals, in 2017. CyDex pharmaceutical is also the holder of DMF 14364 and DMF 20732.

DMF 14364 is a type V DMF. This type of DMF contains accepted FDA reference information.[8] There are 11 in vitro reports of clinical studies located in section 5 of this drug master file. Salient information from these studies is presented in Appendix 10.6, *Summary Table DMF 14364, Clinical Data Entry Content with Assessment of Relevance*. From among the eleven clinical study entries in the DMF, (b) (4) these are not relevant to the proposed product. (b) (4) this was also not relevant to the proposed product. (b) (4) was insufficient for acceptable support of the proposed product.

The remaining study (section 5.3.3.2 ; 150-225) had a 200mg/kg Captisol dose sequence where 4 subjects, in this single dose cohort, achieved infusion rates >250mg/min. These subjects weighed 79.4kg, 78.4kg, 75.7kg, and 76kg with infusion rates of 263mg/min, 260mg/min, 253mg/min, and 253mg/min respectively. This study contained descriptive safety narratives for subjects who had adverse effects or laboratory abnormalities. There was individual subject level dosing data. There were group mean baseline to post captisol infusion vital sign and laboratory data. Complete subject level data for vital signs and laboratory studies were not present. This

[8] FDA Drug Master Files: Guidelines, https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm122886.htm

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study contains the most comprehensive safety assessment for captisol infusion with high maximum infusion rates. However, the infusion rate, although high, was at maximum 12% less than the proposed product. In addition, the 4 subjects with infusion rates > 250mg/min (83.4% of proposed product) received only a single dose. All these subjects were male.

Reviewer Comment: The DMF has insufficient support for Captisol safety. tn. A single clinical entry in the DMF, study 150-225 has the most extensive total exposure and rate of exposure in healthy volunteers with instances of dosing greater than 84% of the rate for the proposed product but safety data are insufficient see Appendix 10.6, Table 21.

The applicant literature review covered 15 references (see Appendix 10.7, *Summary Table of Sponsor Literature References, Clinical Data Content with Assessment of Relevance* These are examined for relevant high infusion rates of captisol, similar or greater total captisol dose than the proposed product. The quality of safety data content is also assessed. In 14 of 15 references there was insufficient dose rate, dose data, or safety data. In a single study of carfilzomib in multiple myeloma patients there are high captisol deliver rates because each mg of API delivers 50mg of Captisol. However, the study is not adequate to contribute to the use of captisol in the proposed product due to absence of patient level safety data to assess the patient cohort with normal renal function. In addition, there is no patient level data for dose / infusion rate by renal function strata, although it is possible that individual patients may have reached both infusion rate > 300mg/min and a sufficient total daily captisol dose to match the proposed product.

Summation of Intravenous Exposures

Study A98

There were 34 single dose 10mg/kg infusions of the test product (captisol-fosphenytoin) where the infusion rate was 300mg/min. In study A98 mean and median weight were 71.1kg and 70kg respectively. Based on the mean weight, the mean test product total dose was 711mgPE with a delivery of 1422mg Captisol.

DMF14364 Relevant Entries

One clinical entry is identified with partial safety data and 4 single dose exposures with a rate >250mg/min (84% of proposed) that delivered a mean total dose of 15450mg (15.45 grams) for these 4 exposures.

Sponsor Literature Presentation

In the study by Badros et. al. these patients received 27mg/m^2 of carfilzomib from treatment cycle 3 to 12. This delivers, with an average BSA of 1.9$m^{2,}$ a total 2565mg Captisol. The

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carfilzomib infusions are administered over 2 to 10 minutes, however patient level data is not provided so there are no specific infusion rates. Only a range of infusion rates can be inferred. This range is from 1282mg/min for a 2 min infusion and 257mg/min for a 10min infusion rate. Although these instances of Captisol infusion are in near parity with those of the proposed product, there is insufficient safety data to use these exposures for safety support.

Conclusion, Captisol Exposures:

Although there were some relevant instances of Captisol exposure (infusion rate and total dose), none were sufficient in all elements of infusion rate, total dose or completeness of safety information to provide adequate support for the proposed product indications. Overall, in the 3 sources of Captisol exposure presented in the submission (including Captisol DMF 14364, the published literature presentation, and the exposures in study A98), there was insufficient clinical content to support the safety of the Captisol dosing for the proposed indications.

7.6. Safety Analyses by Demographic Subgroups

The applicant reports no subgroup analyses were performed in study 247 or A98.

7.7. Specific Safety Studies/Clinical Trials

None.

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

Not applicable- reliant on Cerebyx

7.8.2. Human Reproduction and Pregnancy

Not applicable- reliant on Cerebyx

7.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable- reliant on Cerebyx

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable- reliant on Cerebyx

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7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable- reliant on Cerebyx

7.9.2. Expectations on Safety in the Postmarket Setting

Not applicable- reliant on Cerebyx

7.9.3. Additional Safety Issues From Other Disciplines

None.

7.10. Integrated Assessment of Safety

Summary

There were no deaths in the bioequivalence studies. There was a single SAE in a subject who was administer reference drug in excess of a dose of 1500 mgPE/kg (fosphenytoin) and experienced lightheadedness. The subject had a weight of 92 kg so the dose was within the boundary of an adult loading dose. Examination of the TEAE from pooled studies A98 and 247 revealed the most frequent adverse event preferred term associated with both test and reference treatment was “dizziness”. The preferred terms with a frequency >10% in association with either test or reference product treatment were “dizziness”, “paraesthesia”, “pruritus”, “headache”, “somnolence”, “ataxia”, “nausea” and “hypoacusis”. Treatment-emergent adverse events from Study A98 were examined separately. In this study, there were three terms with an excess in the test product over the reference product; these terms were “dizziness”, “visual impairment” and “fatigue” with an excess, in percent, over the reference product of 2.3%, 3.5% and 2.4% respectively. Overall the test product does not reveal a notable difference in safety from the reference product based on examination of the treatment emergent adverse effects.

In study 247 period 2, examination of group mean change in values for hematology and clinical chemistry parameters between baseline and post-injection of test product reveal no clinically significant change associated with test product treatment. When compared with the group mean changes in reference product, there is no notable difference in the group mean changes in hematology and clinical chemistry parameters between the test and reference product injections. Examination of hepatic and renal outliers do not reveal evidence of a safety signal associated with test product. Examination of mean change in beta 2 microglobulin reveals no clinically meaningful change from baseline to post treatment values.

In study A98 the examination of group mean change in clinical chemistry parameters from baseline to treatment reveals no notable change associated with test or reference drug

infusion. Examination of group mean change of hematology parameters reveals no notable change from baseline to test drug treatment. Outlier examination of hematology parameters reveals notable change in several WBC and neutrophil counts. These observations did not reveal a trend clearly related to test or reference product, and there were no preferred term entries in the adverse events dataset related to infections. A myelosuppressive effect is identified in reference drug labeling (fosphenytoin) including leukopenia, granulocytopenia, agranulocytosis, and pancytopenia. The observed decline in WBC and neutrophil count are consistent with this labeled property of phenytoin. Examination of the selected chemistry parameters did not reveal notable outliers in the ALT, BUN, Creatinine, Glucose, Sodium and Total Bilirubin datasets. Examination of mean urine beta 2 microglobulin levels for test product in period 2 of sequence BA reveal a 169% increase in the group mean value at day 14 post infusion. This was found to be driven by a single patient with an anomalous low period 2 baseline but does not represent an authentic elevation of post treatment beta 2 microglobulin levels. Overall in study A98, no new safety signal is identified for the fosphenytoin-captisol product based on examination of study A98 laboratory parameters.

Examination of systolic blood pressure was performed in study A98. There were no differences in mean systolic blood pressures identified following test product infusion compared to reference product infusion. When outliers with low post-infusion systolic blood pressure following test product infusion were compared with post-infusion reference product low outliers, those following test product were lower. The frequency of low outliers was similar between test and reference post infusion groups. In study 247 there was no clear difference in low outlier magnitude or frequency and no group mean test and reference product differences. In both study A98 and 247 there was a post-infusion trend toward lower systolic and diastolic blood pressure values in associated with both test and reference products.

Overall the metrics that were observed to shift toward abnormal values in these bioequivalence studies were the same metrics that are known safety issues in treatment with phenytoin injection (fosphenytoin and phenytoin). These include a tendency toward myelosuppression and hypotension. There is no differential safety signal identified between test and reference product in the bioequivalence studies.

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8. Labeling Recommendations

8.1. Prescription Drug Labeling

Proposed labeling is identical to the listed drug, Cerebyx, except at four entries that are relevant to the change in excipient. These four entries are in section 2.2 “Preparation” where room temperature storage is permitted

Since none of the proposed indications are adequately supported by clinical safety data, there were no labeling negotiations held with the applicant in this review cycle.

8.2. Nonprescription Drug Labeling

Not applicable.

9. Postmarketing Requirements and Commitments

Not applicable since approval is not recommended.

10. Appendices

10.1. References

See footnotes.

10.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Studies A98 & 247

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

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<table>
<tr><td colspan="3">If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in S

Sponsor of covered study: _____</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

10.3. A98 Study Report Reference Range Tables

Figure 7 Study A98 Hematology Reference Range

Reference Range - Hematology

Effective: 08/19/05

Parameter	Sex	Age	Range
WBC	M / F	> 14Y	4.0 – 10.5 x 10^3/µL
RBC	F	> 14Y	3.80 – 5.10 x 10^6/µL
	M	> 14Y	4.10 – 5.60 x 10^6/µL
HGB	F	> 14Y	11.5 – 15.0 g/dL
	M	> 14Y	12.5 – 17.0 g/dL
HCT	F	> 14Y	34 – 44 %
	M	> 14Y	36 – 50 %
MCV	F	> 14Y	80 – 98 fL
	M	> 14Y	84 – 96 fL
MCH	M / F	> 14Y	27 – 34 pg
MCHC	M / F	> 14Y	32 – 36 g/dL
RDW	M / F	> 14Y	11.7 – 15.0 %
Platelets	M / F	> 14Y	140 – 415 x 10^3/µL
Neutrophils%	M / F	> 14Y	40 – 74 %
Lymphocytes%	M / F	> 14Y	14 – 46 %
Monocytes%	M / F	> 14Y	4 – 13 %
Eosinophils%	M / F	> 14Y	0 – 7 %
Basophils%	M / F	> 14Y	0 – 3 %
Neutrophils#	M / F	> 14Y	1.8 – 7.8 x 10^3/µL
Lymphocytes#	M / F	> 14Y	0.7 – 4.5 x 10^3/µL
Monocytes#	M / F	> 14Y	0.1 – 1.0 x 10^3/µL
Eosinophils#	M / F	> 14Y	0.0 – 0.4 x 10^3/µL
Basophils#	M / F	> 14Y	0.0 – 0.2 x 10^3/µL

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Figure 8 Study A98 Chemistry Reference Range

Reference Ranges - Chemistry

Effective: 08/19/05

α 1 - acid glycoprotein [8]	0.5 – 1.2 g/L
Albumin	3.4 – 4.7 g/dL
Alkaline Phosphatase	34 – 122 U/L
ALT (SGPT	7 – 48 U/L
AST (SGOT)	14 – 45 U/L
BUN	6 – 24 mg/dL
Calcium [1]	8.7 – 10.7 mg/dL
Cholesterol [4]	0 – 200 mg/dL
Creatine Kinase (CK)	0 – 222 U/L
Chloride	101 – 110 mmol/L
Carbon dioxide (bicarbonate) [1]	18 – 33 mmol/L
Creatinine [2]	0.3 – 1.4 mg/dL
Direct Bilirubin	0.0 – 0.2 mg/dL
GGT (Gamma Glutamyltransferase) [3]	Male: 0 – 61 U/L Female: 0 – 36 U/L
Globulin (calc) [6]	2.0 – 4.4 g/dL
Glucose (Ref range: Non-fasting) [10]	78 – 121 mg/dL
Glucose (fasting) [11]	65 – 99 mg/dL
HDL-C [4]	40 – 150 mg/dL
Iron [7]	Male: 54 – 182 µg/dL Female: 35 – 156 µg/dL
IgA [9]	71 – 379 mg/dL
IgG [9]	658 – 1643 mg/dL
IgM [9]	40 – 265 mg/dL
Potassium	3.2 – 5.7 mmol/L
LDH	124 – 243 U/L
LDL-C (calc) [4]	0 – 130 mg/dL
LDL-C (direct) [12]	0 – 130 mg/dL
Magnesium [1]	1.7 – 2.6 mg/dL
Sodium [2]	140 – 155 mmol/L
Non-HDL-C (calc) [4]	0 – 160 mg/dL
Phosphate (inorganic) [5]	2.2 – 5.1 mg/dL
Total Bilirubin	0.3 – 1.1 mg/dL
Total Protein	6.0 – 8.5 g/dL
Triglyceride [4]	0 – 150 mg/dL
Uric Acid	2.6 – 8.1 mg/dL

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10.4. β2-microglobulin as a Renal Biomarker

Beta-2 microglobulin (B2M) is a protein that is found on the surface of nucleated cells (contain a nucleus) and functions as part of the human immune system. This protein is routinely shed by cells into the blood and is present in most body fluids, with highest levels in the blood, generally lower levels in spinal fluid, and trace levels in urine.

In the kidneys, B2M passes through blood-filtering units called the glomeruli and is then reabsorbed by the renal proximal tubules, structures that reclaim water, proteins, vitamins, minerals, and other vital substances. Normally, only small amounts of B2M are present in the urine, but when the renal tubules become damaged or diseased, B2M concentrations increase due to the decreased ability to reabsorb this protein. When the glomeruli in the kidneys are damaged, they are unable to filter out B2M, so the level in the blood rises.

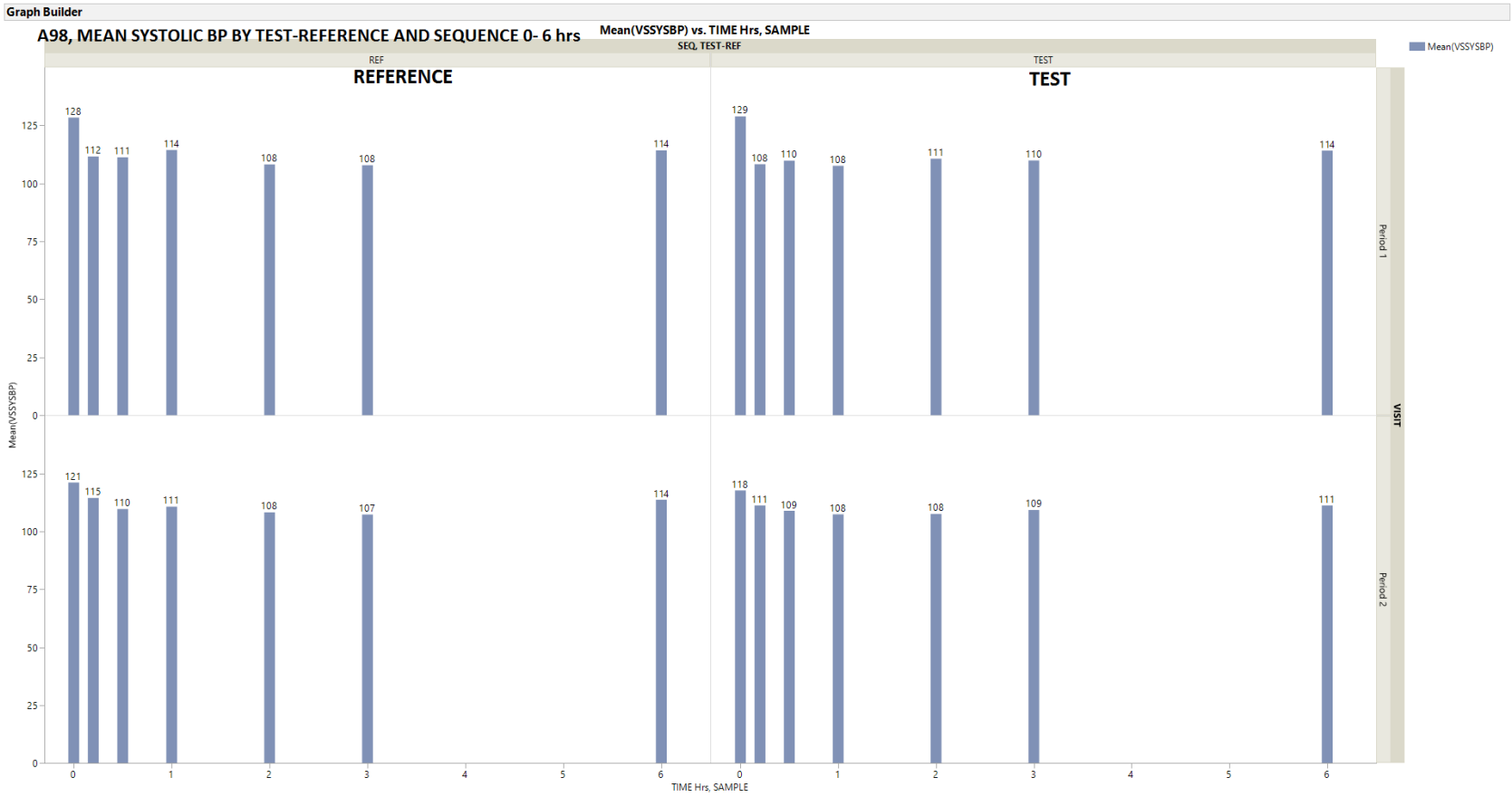
Acute kidney injury is a common clinical syndrome that is characterized by a rapid decline in kidney function, often triggered by glomerular disease and/or tubulointerstitial disease and associated with high morbidity and mortality. In addition to serum creatinine, β2-microglobulin is a biomarker that can be used to determine underlying causes of acute kidney injury. Serum β2-microglobulin derives from cellular membrane turnover [6], since β2-microglobulin forms the invariant light chain portion of major histocompatibility complex (MHC) class I in membranes of all cells. As a single-chain small polypeptide (MW = 11.8 kDA), β2-microglobulin is filtered almost completely through the glomeruli of the healthy kidney and then reabsorbed by the renal proximal tubules. Only a small amount of β2-microglobulin can be detected in the urine under normal physiological conditions. Therefore, levels of serum and urinary β2-microglobulin reflect the functions of glomeruli and proximal tubules. In patients with acute kidney injury, an increase in serum creatinine, together with an increase in urinary β2-microglobulin, strongly suggests proximal tubule injury. On the other hand, an increase in serum creatinine with elevated serum β2-microglobulin is seen in patients with decrease in glomerular filtration rate. Elevated urinary β2-microglobulin was associated with tubular injury caused by viral infection, ischemia, and toxicity from medications or heavy metals.[9]

[9] Xu Zeng, Deloar Hossain, David G. Bostwick, Guillermo A. Herrera, and Ping L. Zhang, "Urinary β2-Microglobulin Is a Good Indicator of Proximal Tubule Injury: A Correlative Study with Renal Biopsies," Journal of Biomarkers, vol. 2014, Article ID 492838, 7 pages, 2014. https://doi.org/10.1155/2014/492838.

Reference ID: 4406956

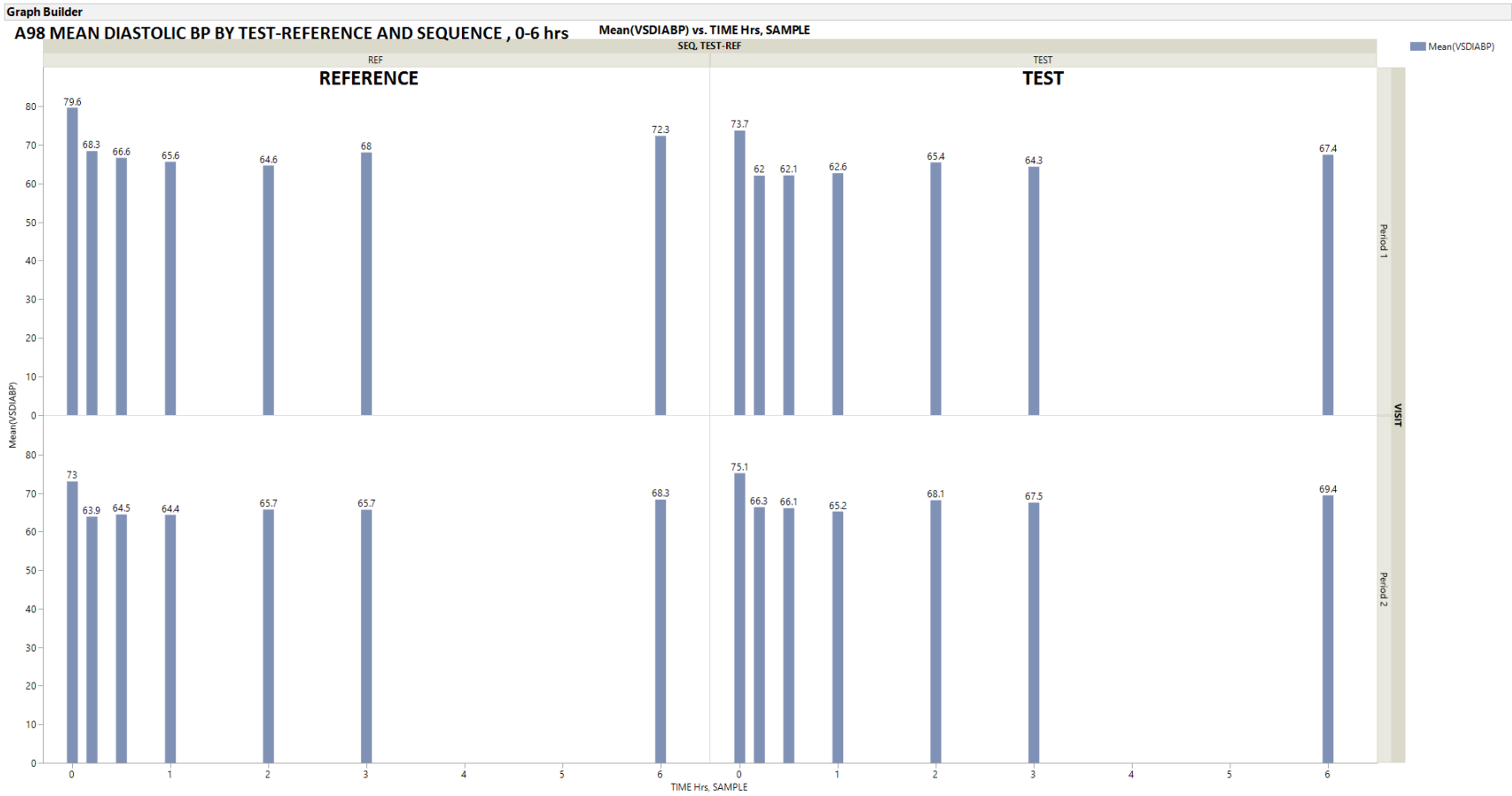
10.5. Vital Signs, Group Mean Systolic Blood Pressure, Minimum Systolic & Diastolic Pressure by Group

Figure 9 Study A98, Mean Group Systolic Blood Pressure, Test- Reference by Study Hour (Baseline to 6 hour post infusion)



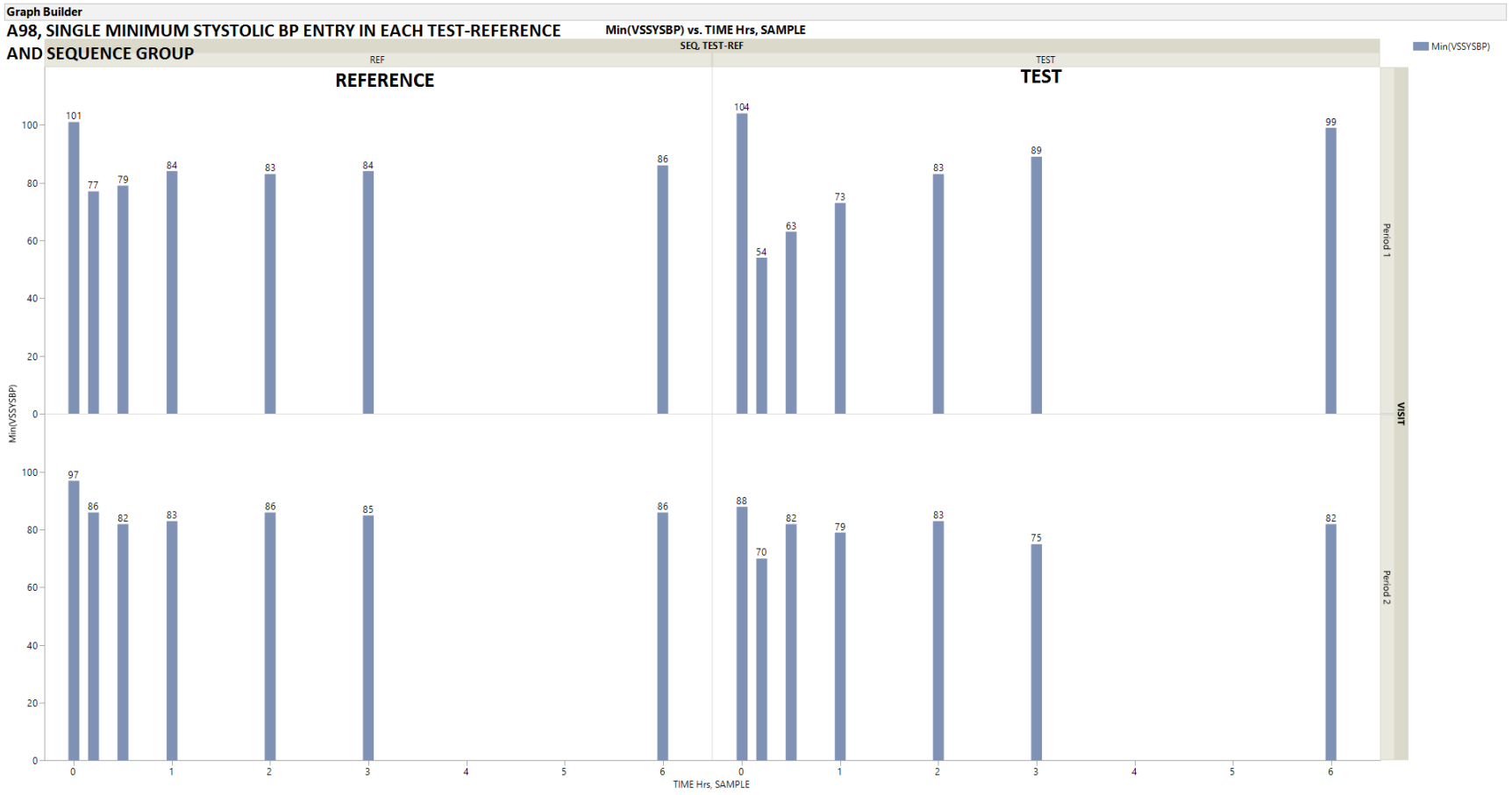
Reference ID: 4406956

Figure 10 Study A98, Mean Group Diastolic Blood Pressure, Test- Reference by Study Hour (Baseline to 6 hour post infusion)



Reference ID: 4406956

Figure 11 Study A98 Group Minimum Systolic Blood Pressure (single value), Test – Reference by Study Hour (Baseline to 6hr Post Infusion)



Reference ID: 4406956

Table 19 Study A98, Group Mean and Median Systolic & Diastolic Blood Pressure with Group Single Value minimum measures by Time and Test or Reference Product

TIME Hrs, SAMPLE, Study A98	SEQ	# SUBJECTS	SEQ, TEST-REF	MEAN SYSTOLIC	MEAN DIASTOLIC	MEDIAN SYSTOLIC	MEDIAN DIASTOLIC	MINIMUM SYSTOLIC	MINIMUM DIASTOLIC
0	AB	19	TEST	129	74	129	76	104	63
0.2	AB	19	TEST	108	62	112	62	54	23
0.5	AB	19	TEST	110	62	110	64	63	35
1	AB	19	TEST	108	63	106	62	73	43
2	AB	19	TEST	111	65	114	65	83	53
3	AB	19	TEST	110	64	111	67	89	50
6	AB	19	TEST	114	67	116	67	99	55
0	BA	19	REF	121	73	124.5	71	97	63
0.2	BA	19	REF	115	64	116	65	86	45
0.5	BA	19	REF	110	64	111	64	82	47
1	BA	19	REF	111	64	111	64	83	47
2	BA	19	REF	108	66	109	68	86	48
3	BA	19	REF	107	66	109	67	85	51
6	BA	19	REF	114	68	117	68	86	56
0	AB	15	REF	128	80	125	77	101	67
0.2	AB	15	REF	112	68	112	69	77	51
0.5	AB	15	REF	111	67	114	68	79	51
1	AB	15	REF	114	66	111	64	84	53
2	AB	15	REF	108	65	109	63	83	52
3	AB	15	REF	108	68	114	69	84	56
6	AB	15	REF	114	72	112	74	86	55
0	BA	15	TEST	118	75	119	72	88	60
0.2		15	TEST	111	66	113	69	70	41
0.5		15	TEST	109	66	109	66	82	43
1		15	TEST	108	65	108	66	79	47
2		15	TEST	108	68	108	67	83	53
3		15	TEST	109	68	108	67	75	47
6		15	TEST	111	69	113	69	82	54

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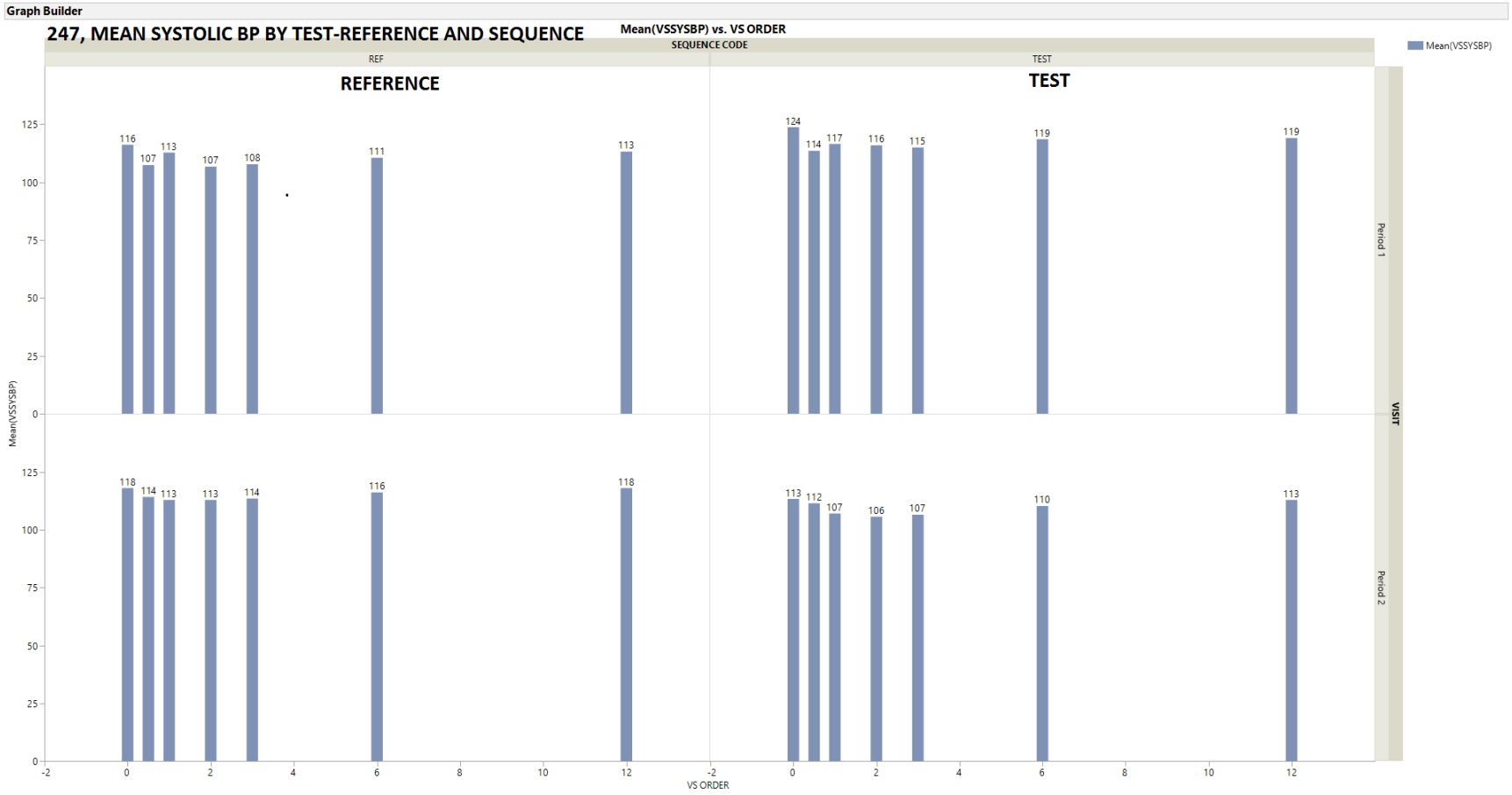
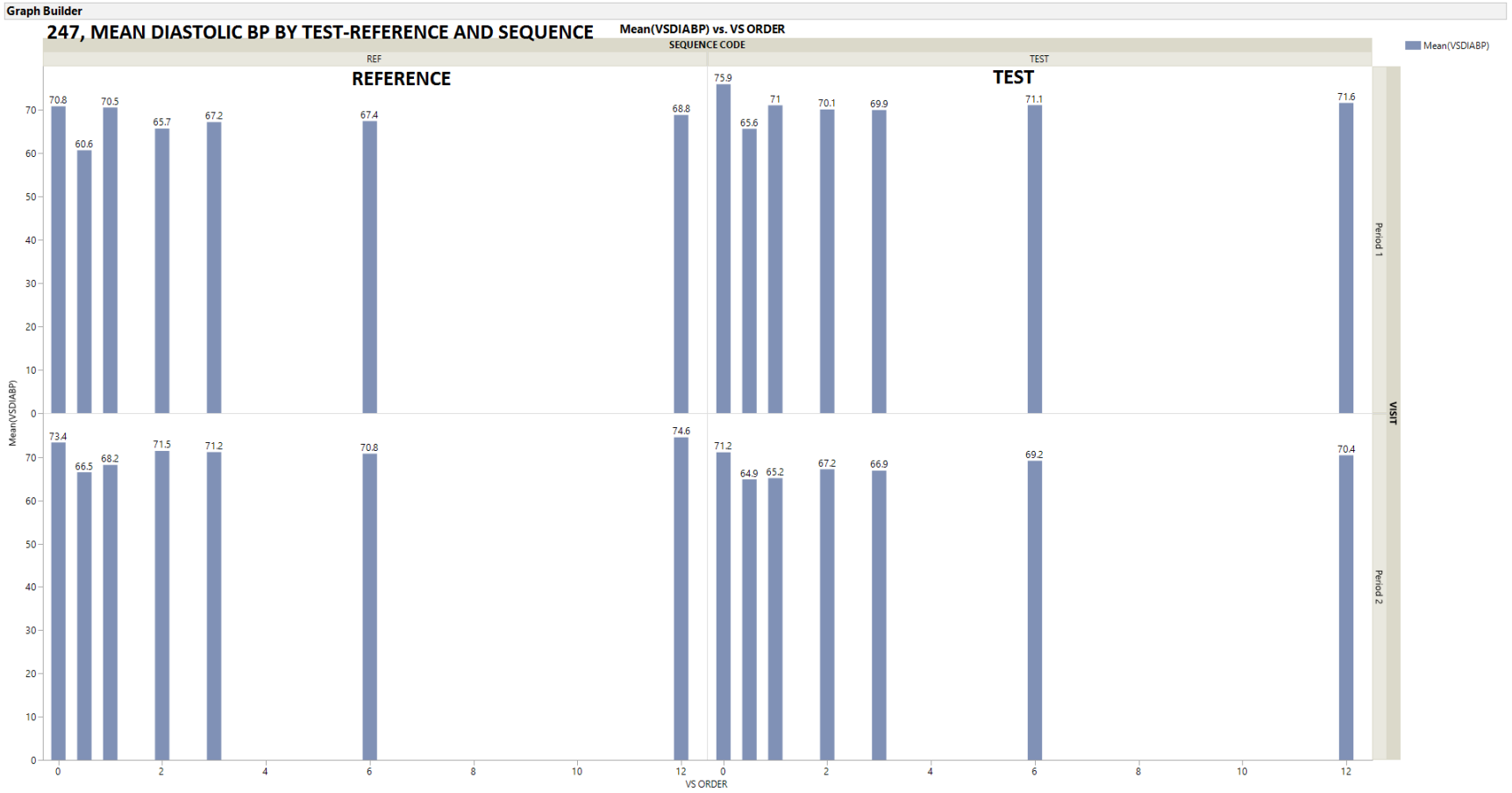
Figure 12 Study 247, Mean Group Systolic Blood Pressure, Test- Reference by Study Hour (Baseline to 6 hour post infusion)



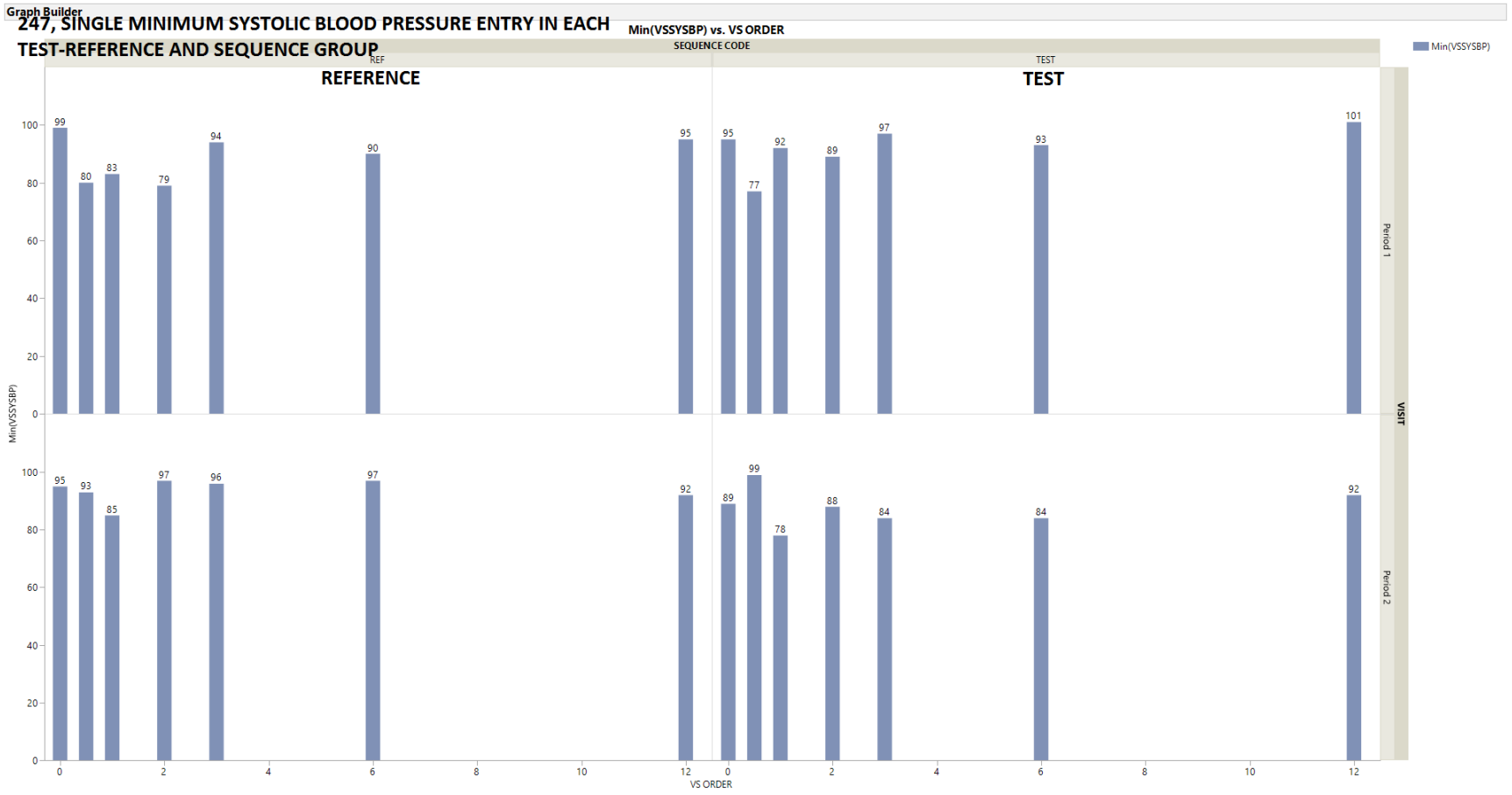
Reference ID: 4406956

Figure 13 Study 247, Mean Group Diastolic Blood Pressure, Test- Reference by Study Hour (Baseline to 6 hour post infusion)



Reference ID: 4406956

Figure 14 Study 247 Group Minimum Systolic Blood Pressure (single value), Test – Reference by Study Hour (Baseline to 6hr Post Infusion)



Reference ID: 4406956

Table 20 Study 247, Group Mean and Median Systolic & Diastolic Blood Pressure with Group Single Value Minimum Measures by Time and Test or Reference Product

TIME Hrs, SAMPLE, STUDY 247	SEQUENCE	# SUBJECTS,	SEQ, TEST-REF	MEAN SYSTOLIC	MEAN DIASTOLIC	MEDIAN SYSTOLIC	MEDIAN DIASTOLIC	MINIMUM SYSTOIC	MINIMUM DIASTOLIC
0	AB	25	TEST	124	76	125	75	95	61
0.5	AB	25	TEST	114	66	114	66	77	44
1	AB	25	TEST	117	71	119	72	92	43
2	AB	25	TEST	116	70	116	70	89	55
3	AB	25	TEST	115	70	113	69	97	59
6	AB	25	TEST	119	71	117	71	93	57
12	AB	25	TEST	119	72	117	70	101	61
0	BA	25	REF	116	71	116	68	99	48
0.5	BA	25	REF	107	61	103	59	80	46
1	BA	25	REF	113	71	109	69	83	49
2	BA	25	REF	107	66	105	66	79	35
3	BA	25	REF	108	67	105	68	94	51
6	BA	25	REF	111	67	106	66	90	54
12	BA	25	REF	113	69	113	66	95	57
0	AB	25	REF	118	73	117	73	95	60
0.5	AB	25	REF	114	67	114	66	93	57
1	AB	25	REF	113	68	112	68	85	54
2	AB	25	REF	113	71	112	70	97	59
3	AB	25	REF	114	71	113	69	96	62
6	AB	25	REF	116	71	116	72	97	47
12	AB	25	REF	118	75	118	74	92	58
0	BA	25	TEST	113	71	108	70	89	51
0.5	BA	25	TEST	112	65	110	65	99	47
1	BA	25	TEST	107	65	107	65	78	45
2	BA	25	TEST	106	67	106	65	88	51
3	BA	25	TEST	107	67	105	67	84	48
6	BA	25	TEST	110	69	108	69	84	55
12	BA	25	TEST	113	70	113	71	92	58

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