CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213645Orig1s000

NON-CLINICAL REVIEW(S)

Division of Anti-Infective Products

Memorandum to the file for NDA 213645

Date: 12/17/2021

From: Ines Pagan, DVM, PhD

Pharmacology/Toxicology reviewer

To: NDA 213645

Through: Terry Miller, PhD

Pharmacology/Toxicology supervisor

Re: Review of Toxicological Assessments for Qualification of Leachables in Dapzura for injection in NDA 213645 Resubmission

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In the NDA 213645 resubmission (June 14, 2021), in response to FDA's Complete Response Letter, the Applicant provided sufficient nonclinical data recommended to address the deficiencies identified in 5 unqualified leachables (b) (4) detected in a leachables assessment (b) (4) (b) (4) The response included primary sources of toxicological information and bioavailability information for the individual leachables to account for route-to-route extrapolations for toxicological studies conducted by routes of exposure other than the intended intravenous exposure for Dapzura for injection. Based on considered No Observed Adverse Effect Levels (NOAELs) or Lowest Observed Adverse Effect Levels (LOAELs) from published toxicological studies, Permissible daily Exposure (PDE) levels for the 5 leachables and margins to the maximum potential exposure to patients administered Dapzura for injection were calculated (See Reviewer Table 1 below). The maximum potential exposure of patients to leachables in Dapzura are provided in Table 2 for reference. The PDE levels of the individual leachables were calculated in accordance with methods for establishing exposure limits described in ICH Guidance Q3C(R8)[1], using the following formula:

PDE = NOAEL/LOAEL x Weight Adjustment (50 kg)[2]/ Modifying Factors (F1-F7)[3]

Given that the individual leachables toxicological assessments were considered adequate and that the calculated PDEs have reasonable exposure margins to the maximum potential leachable exposure to patients administered Dapzura, these leachables are unlikely to pose

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[1] Guidance Document Q3C(R8) Impurities: Guidance for Residual Solvents Guidance for Industry (December 2021). Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3cr8-impurities-guidance-residual-solvents-guidance-industry.

[2] A conservative 50 kg human assumption was used in the PDE calculation.

[3] Uncertainty Factors are used to account for the following: extrapolation between species, variability between individuals, short term exposure in toxicological studies, cases where severe toxicity is observed, NOAEL not established, different route of administration or when a surrogate compound is used.

significant risks to humans and are considered qualified from a pharmacology/toxicology perspective.

Table 1. Summary of Maximum Leachable Exposures and Exposure Margins Considered for Qualification

Leachable (CAS#)	Surrogate	Study	NOAEL/ LOAEL (mg/kg)	PDE (µ/day)	Maximum Leachable Exposure (µ/day)*	Exposure Margin (fold)	Qualification
(b) (4)							yes
							yes
							yes
							yes
							yes

(Reviewer Table. Surrogate and study references taken from Study Report BXU562758 and/or Quality Information Amendment Resubmission- Response to Complete Response Letter Dated April 29, 2021; NOAELs/LOAELs determined from studies submitted in the Response to Complete Response Letter Dated April 29, 2021; Maximum Leachable Daily exposure from Table 2 below; PDE and exposure margins calculated according to ICH Guidance Q3C(R8)).

*Maximum leachable Exposure (µ/day) calculated using an assumption of a 70 kg adult to be comparable to the Applicant's calculation.

Table 2. Maximum Potential Daily Exposure of Patients to Leachables in Dapzura for Injection Across Patient Populations

Patient Population*	Max daily dose (mg/kg)	Max daily dose (mL)	(b) (4) (µg/mL)	(b) (4) (µg/mL)	(b) (4) (µg/mL)	(b) (4) (µg/mL)	(b) (4) (µg/mL)
Adults (70kg)	6	8.4	(b) (4)				
Peds 12-17	5	6.4					
Peds: 7 - 11 Years (35.6kg)	7	5.0					
Peds: 2 - 6 Years (20.6kg)	9	3.7					
Peds: 1 - <2 Years (12.5kg)	10	2.5					
Adults (60kg)	6	7.2					

(b) (4)

(Reviewer Table. *Maximum potential daily exposures in patient populations calculated based on the levels of leachables detected in Dapzura for injection (22 months leachables analysis values taken from Table 1 in Study Report BXU562758; maximum daily dose or Daptomycin for patient populations taken from Table 11 Study Report BXU562758).

Reviews of the most robust information from the individual toxicological studies used in the leachables toxicological assessments and the general approach to the calculation of the Permissible Daily Exposure levels of the individual leachables (b) (4) are summarized below.

(b) (4)

Due to the limited published toxicological information, the Applicant identified (b) (4) as a surrogate (b) (4) based on similarity in physicochemical properties to (b) (4) with available primary source toxicological information. The CDER/OTS/OCP/DARS consult with the Computational Toxicology Consultation Service (CTCS) found this surrogate acceptable.

The toxicity (b) (4) was evaluated in a GLP, 2-year toxicology and carcinogenesis inhalation study in rats and mice conducted by (b) (4)

Study Title (b) (4)

Methods

Male and female rats and mice (10/sex/group 14-week study; 50/sex/group 2-year study) were administered (b) (4) by the inhalation route at 0, 500, 1000, 2000, 4000 and 8000 ppm for 6 hours, 5 days per week for 14 weeks or to 0, 500, 2000 and 8000 ppm for 2 years. Animals were observed twice daily and detailed clinical findings were recorded weekly and animals were weighed pre-dose, weekly

(b) (4)

during the study and prior to euthanasia. Hematology and clinical chemistry were evaluated in rats at days 3 and 23 and at euthanasia. Complete histopathology of collected tissues was performed in all rats and mice. Sperm motility evaluated in all males and vaginal cytology evaluated in all females in the 14-week range finding study. A biomarker of exposure (2-hydroxyisobutyric acid in urine) was evaluated at 6, 12 and 18 months in the 2-year study.

Results

Rat 14-Week Dose Finding Study (inhalation)

- There were no unscheduled deaths or notable clinical findings
- There were no body mean weight differences between treated and control animals and no hematological or clinical chemistry findings
- There were no reproductive findings in males or females
- Increased kidney weight observed at 4000 and 8000 ppm (absolute and relative weight of increases 10% and 8%, respectively) in males. Increased absolute liver weights of females ≥ 1000 ppm and relative liver weights observed in all treated females (20%). There were no gross or microscopic correlates to the increased kidney or liver weights in rats
- There were no test article related gross pathological findings. Microscopic findings included minimal hypertrophy of goblet cells of the nasopharyngeal tissues (non-adverse) observed in some animals of all treated groups (males and females)

Mice 14-Week Dose-Finding Study (inhalation)

- There were no unscheduled deaths or notable clinical findings
- There were no body mean weight differences between treated and control animals and no hematological or clinical chemistry findings
- There were no reproductive findings in males or females
- Increased absolute and relative kidney weights observed at 8000 ppm in males (~11%) and females (~18%). There were no gross or microscopic correlates to the increased kidney weight in mice
- Genetic toxicology. (b) (4) did not induce micronucleated erythrocytes in mouse peripheral blood cells

Rat 2-Year Carcinogenicity Study

- There were no test article related unscheduled deaths
- There were no changes in body weights compared to controls
- Microscopic changes included olfactory epithelial hyaline degeneration with slightly higher severity than control at 2000 and 8000 ppm in males and females (severity control 1.3 compared to 2.2 and 2.6 at 2000 and 8000 ppm, respectively). Hyaline degeneration was characterized by accumulation of eosinophilic globules in the olfactory epithelium likely due to inhalation of irritant material

- Thyroid gland follicular carcinoma was observed in males at 8000 ppm that was of slightly higher incidence than control group (2% control versus 10% at the high dose) and higher than historical controls. There were no neoplastic findings in female rats
- NOAEL considered at 2000 ppm based on thyroid follicular carcinoma observed in males at 8000 ppm

Mice 2-Year Carcinogenicity Study

- There were no test article related unscheduled deaths
- Slight decreases in body weights were observed in female mice at 2000 and 8000 ppm compared to controls. No changes in body weights were observed in male mice
- Microscopic changes included respiratory hyaline degeneration in all treatment groups and olfactory epithelial hyaline degeneration of slightly higher incidence in males and females at 2000 and 8000 ppm
- NOAEL considered at 8000 ppm

Reviewer Approach to Calculation of (b) (4) PDE

Uncertainty factors applied:

F1 (between species) = 5 (rat to human)

F2 (between individuals) = 10

F3 (exposure duration) = 1

F4 (severe toxicity) = 1

F5 (NOAEL not established) = 1

F6 (different route, bioavailability) = (b) (4)

F7 (surrogate) = (b) (4)

PDE = NOAEL x Weight Adjustment (50 kg)[10]/ Uncertainty Factors (F1-F7)[11]

PDE = (b) (4) mg/kg/day x 50 kg / (b) (4) = (b) (4) mg or (b) (4) µg/day

Conclusion

The (b) (4) PDE derivation was based on a NOAEL in rats (considered the most sensitive species) from an adequate study of an acceptable surrogate (b) (4) In addition to recommended standard modifying factors (F1-F4), a conservative modifying factor (F6) (b) (4) (recommended for assumption of

[10] A conservative 50 kg human assumption was used in the PDE calculation.
[11] Uncertainty Factors are used to account for the following: extrapolation between species, variability between individuals, short term exposure in toxicological studies, cases where severe toxicity is observed, NOAEL not established, different route of administration or when a surrogate compound is used.

[redacted]%) was used to account for the limited data on bioavailability by the oral route [redacted] and a modifying factor (F7) [redacted] for the use of a surrogate with a total denominator of [redacted] A margin of exposure to the maximum potential level of exposure (assuming a 70 kg human) of [redacted]-fold was considered adequate. From a pharmacology/toxicology perspective [redacted] in Dapzura for injection is considered adequately qualified.

[redacted]

The toxicity [redacted] was evaluated in 3-month repeat dose gavage toxicity studies in rats and mice conducted [redacted]

Study Title:

1- **3-Month Evaluation of the Toxicity [redacted] in F344/N Rats Exposed via Gavage**
2- **3-Month Evaluation of the Toxicity [redacted] in B6C3F1 Mice Exposed via Gavage**

Methods

[redacted] was administered by oral gavage to rats (Fisher 344; 10/sex/group) and mice (B6C3F1; 10/sex/group) at 0, 75, 150, 300, 600 and 1,200 mg/kg/day for 3 months. Mortality, clinical signs, body and organ weights were reported.

Results

<u>3-Month Study in F344 Rats</u>

- Dose dependent test article mortality was observed in males (3/10, 6/10, 9/10, 8/10 and 10/10 at 75, 150, 300, 600 and 1,200 mg/kg/day) and females (2/10, 2/10, 4/10, 6/10 and 10/10 at 75, 150, 300, 600 and 1,200 mg/kg/day) at all doses tested.

[redacted]

- Decreased body weight was observed in males and females ranging from -2 to -5% at 150 to 600 mg/kg/day and -15 to -40% at 1,200 mg/kg/day.
- In males, clinical observations included ruffled fur in some animals ≥600 mg/kg/day and red nose, nasal discharge, rales and diarrhea in some animals at 1,200 mg/kg/day.
- In females, clinical observations included rales in some animals ≥ 300 mg/kg/day and salivation and urine stained red in one animal at 1,200 mg/kg/day.
- Histopathological evaluations were not available for this study.

3-Month Study in B6C3F1 Mice

- Mortality was observed at 1200 mg/kg/day in males (4/10) and females (1/10).
- Decreased body weight was observed in males (13%) at 1,2000 mg/kg/day. No changes in body weight were observed in females.
- There were no reported test article related clinical observations in males or females.
- Histopathological evaluations were not available for this study.

Based on consideration of the rat as a more sensitive species and findings at all doses tested (low incidence mortality and slightly reduced body weight) the rat study LOAEL was considered at (b) (4) mg/kg/day.

Reviewer Approach to Calculation of (b) (4) PDE

Uncertainty factors applied:

F1 (between species) = 5

F2 (between individuals) = 10

F3 (exposure duration) = 1

F4 (severe toxicity) = 10 (mortality)

F5 (NOAEL not established) = 10

F6 (different route, bioavailability) = (b) (4)

PDE = LOAEL x Weight Adjustment (50 kg)[14]/ Uncertainty Factors (F1-F7)[15]

PDE = (b) (4) mg/kg/day x 50 kg / (b) (4) = (b) (4) mg or (b) (4) µg/day

Conclusion

[14] A conservative 50 kg human assumption was used in the PDE calculation.
[15] Uncertainty Factors are used to account for the following: extrapolation between species, variability between individuals, short term exposure in toxicological studies, cases where severe toxicity is observed, NOAEL not established, different route of administration or when a surrogate compound is used.

The PDE (b) (4) was derived from a LOAEL (low incidence mortality of unknown nature). In addition to standard recommended modifying factors (F1-F3), a conservative approach was used including modifying factors to account for severe toxicity (F4=10) and a modifying factor to account for the lack of establishment of a NOAEL (F5=10) with a total modifying factor denominator (b) (4) A margin of exposure to the maximum potential level of exposure (assuming a 70 kg human) of (b) (4)-fold in addition of the conservative composite modifying factor denominator (b) (4) was considered reasonable. From a pharmacology/toxicology perspective (b) (4) in Dapzura for injection is considered adequately qualified.

(b) (4)

The toxicity (b) (4) was evaluated in a 13-week repeat dose oral study in Sprague Dawley rats (b) (4)

Study Title: Summaries of Toxicological Data, Toxicological Tests on (b) (4) and other Compounds.

Methods

Sprague Dawley rats (16/sex/group) were exposed to (b) (4) at (b) (4) (males) and (b) (4) (females) mg/kg/day in the feed for 13-weeks. Evaluations included body weights (recorded weekly), food consumption, hematology and histopathological examination of several organs (liver, kidneys, heart, lung, brain, hypophysis, thyroid, adrenals, pancreas testes, epididymis, ovaries, uterus, submaxillary gland, spleen stomach, small intestine, mesenteric lymph node, urinary bladder, sternal marrow, spinal cord and striated muscles).

Results

- No unscheduled deaths or morbidity observed
- Decreased weight gain compared to controls (12%) was observed in females

(b) (4)

- Transient decrease in hematocrit observed at week 7 noted to be within variation observed with control rats in the same laboratory
- No treatment related findings were reported in male rats
- No histopathological changes observed in males or females
- The LOAEL was considered at (b) (4) mg/kg/day, based on decreased weight gain in females

Reviewer Approach to Calculation of (b) (4) PDE

Uncertainty factors applied:

F1 (between species) = 5 (rat to human)

F2 (between individuals) = 10

F3 (exposure duration) = 1

F4 (severe toxicity) = 1

F5 (NOAEL not established) = 10

F6 (different route, bioavailability) = (b) (4)

PDE = LOAEL x Weight Adjustment (50 kg)[17]/ Uncertainty Factors (F1-F7)[18]

PDE = (b) (4) mg/kg/day x 50 kg / (b) (4) = (b) (4) mg or (b) (4) µg/day

Conclusion

The PDE (b) (4) was derived from a LOAEL (based on decreased body weight gains in females). In addition to the standard modifying factors (F1-F4) a modifying factor (b) (4) was used to account for lack of establishment of a NOAEL and a factor (b) (4) to account for limited bioavailability by the oral route with a total modifying factor denominator (b) (4) A margin of exposure to the maximum potential level of exposure (assuming a 70 kg human) of (b) (4)-fold was considered adequate. From a pharmacology/toxicology perspective (b) (4) in Dapzura for injection is considered adequately qualified.

[17] A conservative 50 kg human assumption was used in the PDE calculation.
[18] Uncertainty Factors are used to account for the following: extrapolation between species, variability between individuals, short term exposure in toxicological studies, cases where severe toxicity is observed, NOAEL not established, different route of administration or when a surrogate compound is used.

Due to the limited published toxicological information, the Applicant identified (b) (4) as a surrogate compound based on similarity in physicochemical properties (b) (4) with available primary source information. The CDER/OTS/OCP/DARS consult with the Computational Toxicology Consultation Service (CTCS) found this surrogate acceptable.

The toxicity of (b) (4) (surrogate (b) (4)) was evaluated in a GLP 90-day repeat dose study in beagle dogs (summarized below).

Study Title: 90-Day Oral (Capsule) Toxicity Study with TKA 40016 in Dogs

Methods

The test article ((b) (4) surrogate) toxicity was evaluated in a repeat dose 90-day GLP study in beagle dogs. The test article was administered by the oral route (4/sex/group) at 0, 10, 50, 200 and 1000 mg/kg/day (dosage based on preliminary 14-day range finding study). Animals were observed twice daily for mortality and moribundity. Body weights and food consumption data were collected weekly. Ophthalmic evaluations performed before initiation of the study and at week 13. Blood and urine samples collected for clinical hematology, clinical chemistry and urinalysis before treatment and during weeks 8 and 13 of the study. Macroscopic and microscopic evaluations tissues from each animal in the control and high dose group (livers were evaluated in all animals).

Results

- Overall, the test article was well tolerated in beagle dogs. There were no unscheduled deaths or notable clinical findings
- Sporadic vomiting occurred in some animals including those in the control group (most animals were re-dosed when capsules found in cage)
- Increased liver weight (approximately 40%) observed in males and females at 1000 mg/kg/day
- Liver microscopic findings consisted of minimal to moderate hepatocellular hypertrophy and centrilobular to midzonal cytoplasmic clearance in males and females at 200 and 1000

mg/kg/day, and hepatocellular eosinophilic inclusions in males and females at 1000 mg/kg/day (increased alkaline phosphatase correlate)

- No findings observed at 10 or (b) (4) mg/kg/day
- NOAEL considered at (b) (4) mg/kg/day
- Study appears acceptable with some reservation due to the lack of toxicokinetic data (systemic absorption was reasonably assumed based on the presence of liver findings). This uncertainty was accounted for by application of a modifying factor (F6) (b) (4)

Reviewer Approach to Calculation of (b) (4) PDE

Uncertainty factors applied:

F1 (between species) = 2 (dog to human)

F2 (between individuals) = 10

F3 (differences in time of exposure) = 1 (90-day study which covers ~ 42 days maximum Dapzura treatment period)

F4 (severe toxicity) = 1

F5 (NOAEL not established) = 1

F6 (different route, bioavailability) = (b) (4)

F7 (surrogate) = (b) (4)

PDE = NOAEL x Weight Adjustment (50 kg)[19]/ Uncertainty Factors (F1-F7)[20]

PDE = (b) (4) mg/kg/day x 50 kg /(b) (4) = (b) (4) mg or (b) (4) µg/day

Conclusion

The (b) (4) PDE derivation was based on a NOAEL from an adequate study of an acceptable surrogate (b) (4) In addition to the standard modifying factors (F1-F5), a conservative modifying factor (b) (4) (recommended for assumption (b) (4)) was used to account for the limited data on bioavailability by the oral route (assumed by systemic findings of increased liver weight at the high dose); a modifying factor (b) (4) was used to account for the use of a surrogate (total modifying factor denominator (b) (4)). A margin of exposure to the maximum potential level of exposure (assuming a 70 kg human) of (b) (4)-fold was considered adequate. From a pharmacology/toxicology perspective (b) (4) in Dapzura for injection is considered adequately qualified.

[19] A conservative 50 kg human assumption was used in the PDE calculation.

[20] Uncertainty Factors are used to account for the following: extrapolation between species, variability between individuals, short term exposure in toxicological studies, cases where severe toxicity is observed, NOAEL not established, different route of administration or when a surrogate compound is used.

(b) (4)

The toxicity (b) (4) was evaluated in a reproductive toxicity and developmental study in rats (b) (4)

Study Title: Diverse developmental toxicity (b) (4) in box sexes of rat offspring after maternal exposure during the period from late gestation through lactation (b) (4)

Methods

Maternal Sprague Dawley rats (6-8 dams/group) were exposed to (b) (4) in the feed at 0, 20, 200, 2000 and 10,000 ppm from gestational day (GD) 15 to postnatal day (PND) 21. Body weight and food intake of all dams were recorded at GD 15 and 20 and PND 2, 10 and 21. On PND 2 numbers, weights and anogenital distance were recorded. On PND 3 each litter was culled to 4 males and females; on PND 14 male pups were inspected for changes in the nipples/areolae. Body weights recorded weekly. Dosing was terminated on PND 21; 8 males and 8 females were necropsied at postnatal week (PNW) 11 and 8-10 animals at PNW 20. Prepubertal necropsy was conducted at PND 21 and postpubertal necropsy at PNW 11 and 20 to evaluate weights and multiple organs (brain, pituitary, thyroid gland, liver, kidney, adrenals, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, vagina and mammary glands).

Results

- Findings in Dams

(b) (4)

Slight decrease in body weight gain (-18%) at 20 and 10,000 ppm compared to control. No changes in maternal food consumption observed. No changes in pregnancy duration observed.

- Findings in offspring until prepubertal necropsy

The number of live offspring was no different than controls at any dose tested. Male ratio at birth was reduced at ≥2000 ppm (-20 to -40% lower than controls). In males, anogenital distance reduced (PND2) and retention of nipples/areolae (PND14), slight reduction of body weight, increased relative liver weight, increased relative brain weight and decreased relative testis weights at 10,000 ppm. Decreased absolute testicular wight was reported at 20 ppm but the data was not shown in this publication. In females, decreased relative brain weight observed at 10,000 ppm.

- Findings in onset of puberty and estrous cycle

Preputial separation early onset observed at 200 ppm (driven by 1 male). Extended diestrus 1/8 females at 20 and 200 ppm and 2-4/8 in 2,000 and 10,000 ppm (PNW 8-11) and in 3/10 females at 2000 ppm and 1/10 females at 10,000 ppm (PNW 17-20). Delay of vaginal opening was observed at 10,000 ppm. There were no extended estrous or diestrus in females.

- Findings in adults

In males, slight reduction of relative kidney weight observed at 10,000 ppm. Increased in absolute or relative thyroid weights at ≥20 ppm. In females, decreased pituitary weight observed at 10,000 ppm.

- Histopathology findings

PND 21: liver cell hypertrophy with cytoplasmic eosinophilia in both males and females at 10,000 ppm. In males, dose dependent reduction of spermatocytes development at ≥ 20 ppm, decreased ductular cross sections of the epididymal duct at ≥ 2000 ppm, foci of aggregated Leydig cells at≥ 200 ppm and liver cell hypertrophy at 10,000 ppm. In females, hyperplasia of the mammary gland alveolar bud at ≥ 20 ppm and liver hypertrophy at 10,000 ppm.

PNW 11: in males, loss of testicular germ cell development at ≥ 200 ppm, flattening of the surface epithelial cells of the prostate at 10,000 ppm and mammary gland alveolar cells vacuolar degeneration and atrophy at ≥ 20 ppm. In females, decreased pituitary size at 10,000 ppm.

PNW 20: in males, loss of germ cell development of reduced severity observed at ≥ 20 ppm, mammary gland alveolar vacuolar degeneration and atrophy at ≥ 200 ppm. No findings observed in females.

- Pituitary Immunohistochemistry

Pituitaries of male and females were subject to immunohistochemistry for luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin (PRL). Immunoreactive cells for each hormone were counted (at 400X magnification) and morphometric analysis was conducted after application of a hematoxylin counterstain. PND 21: in males, both FSH and PRL- positive cells were reduced compared to controls and LH-positive cells were increased compared to controls at 10,000 ppm. In females, FSH-positive cells were decreased ≥ 200 ppm, LH-positive cells were increased ≥ 200 ppm

and PRL- positive cells decreased at 10,000 ppm. PNW11: FSH-positive cells were increased in both males and females at 10,000 ppm; PRL-positive cells were unchanged in males and females.

- Based on the findings in males (reduced spermatocyte development in pre-pubertal rats and histopathological changes in the testis and mammary glands) the study LOAEL was considered at (b) (4) ppm ((b) (4) mg/kg).

Reviewer Approach to Calculation of (b) (4) PDE

Uncertainty factors applied:

F1 (between species) = 5 (rat to human)

F2 (between individuals) = 10

F3 (long term exposure) = 1

F4 (severe toxicity) = 5

F5 (NOAEL not established) = 10

F6 (different route, bioavailability) = (b) (4)

PDE = NOAEL x Weight Adjustment (50 kg)[22]/ Uncertainty Factors (F1-F7)[23]

PDE = (b) (4) mg/kg/day x 50 kg / (b) (4) = (b) (4) mg or (b) (4) µg/day

Conclusion

For a conservative derivation of a PDE (b) (4) the study (b) (4) was considered the most appropriate study based on the evaluation of potential reproductive developmental findings at (b) (4) ((b) (4) ppm or (b) (4) mg/kg/day) with the LOAEL considered at (b) (4) mg/kg/day. In addition to standard recommended modifying factors (F1-F4), a conservative factor (F5) of 5 was applied to account for severe toxicity and a factor of 10 (F5) to account for lack of establishment of a NOAEL with a total modifying factor denominator (b) (4) A margin of exposure to the maximum potential level of exposure (assuming a 70 kg human) of (b) (4)-fold was considered adequate. From a pharmacology/toxicology perspective, (b) (4) in Dapzura for injection is considered adequately qualified.

[22] A conservative 50 kg human assumption was used in the PDE calculation.

[23] Uncertainty Factors are used to account for the following: extrapolation between species, variability between individuals, short term exposure in toxicological studies, cases where severe toxicity is observed, NOAEL not established, different route of administration or when a surrogate compound is used.

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	213645
Supporting document/s:	SDN1
Applicant's letter date:	6/30/2020
CDER stamp date:	6/30/2020
Product:	DAPZURA RT (daptomycin) for Injection, 10 ml vial
Indication:	Complicated skin and skin structure infections (cSSSI) and Staphylococcus aureus bloodstream infections, including those with right-sided infective endocarditis
Applicant:	Baxter Healthcare Corporation
Clinical Review Division:	Division of Anti-Infectives (DAI)
Pharm/Tox Division	Division of Pharm/Tox for Infectious Diseases (DPT-ID)
Reviewer:	Ines Pagan, DVM, PhD
Supervisor/Team Leader:	Terry Miller, PhD
Clinical Division Director:	Sumathi Nambiar, MD, MPH
Project Manager:	Carmen DeBellas, RPh, PharmD

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 213645 are owned by Baxter Healthcare Corp. or are data for which Baxter Healthcare Corp. has obtained a written right of reference. Any information or data necessary for approval of NDA 213645 that Baxter Healthcare Corp. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any

data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 213645.

Review Recommendation

The current NDA is recommended for a Complete Response from a pharmacology/toxicology perspective. The Applicant has not provided sufficient safety qualification data for five leachable compounds (b) (4) identified in a leachables assessment with their new drug product. While there are no mutagenicity concerns for any of the identified leachables, the Applicant's safety qualification approach for leachable compounds > 5 mcg/day does not provide adequate information to characterize the general toxicity of the identified leachables.

Nonclinical Deficiency Comment to the Applicant:

You have not provided adequate safety information to support the qualification of the following 5 leachables: (b) (4) The data you provided in your toxicological risk assessment consisted primarily of hyperlinks to public databases (b) (4) with toxicological summaries and conclusions based on unpublished data or proprietary information from Industry not available to the Applicant or FDA for independent review. Therefore, these 5 leachable compounds you have identified in your leachables assessment are not considered adequately qualified for safety.

Information needed to resolve the deficiency

In the absence of sufficient primary toxicity study data available in the published literature or from other available sources needed to conduct a risk assessment for the identified leachables, we recommend you conduct an additional general toxicity study, in an appropriate animal species, for any leachable that exceeds the safety qualification threshold of 5 mcg/day. Such a study should be designed to achieve leachables exposures at clinically relevant levels. We recommend that you submit a draft study protocol for the Agency to review prior to initiating any additional nonclinical studies. By providing a draft protocol for comment, the Agency will be better able to work with you on designing a study that can best inform the safety of the identified leachables when administered at clinically relevant exposures. We also recommend that you submit a leachables assessment plan and/or justification that the leachables in the drug product to be administered to the animals is qualitatively and quantitatively similar to the identified leachables described in Study Report BXU562758. Upon any additional leachables characterization on further testing, should there be any revised structures and/or identification of any structures of leachables compared with those identified in your previous leachables assessment needing qualification (Study Report BXU562758), plan to conduct additional (Q)SAR evaluation(s) for bacterial mutagenicity. A follow-up Ames test (bacterial reverse mutation

assay) is recommended to qualify leachables that exceed 20 mcg/day with identified structural alerts for genotoxic potential.

Executive Summary

Baxter Pharmaceutical Solutions LLC (Baxter) is seeking approval for a new formulation of DAPZURA RT (daptomycin) for Injection, using the 505(b)(2) regulatory pathway. The proposed drug product is intended to be a copy of the listed drug (LD), Cubicin RF (daptomycin for injection, NDA 21572, Merck) available as a lyophilized powder intended for reconstitution with a suitable intravenous solution prior to administration. The Applicant's new drug product contains the same active ingredient, daptomycin, and is intended for use via the same route of administration (intravenous), dosage form and indications as the LD. However, the Applicant's formulation contains new excipients mannitol and sorbitol which are not present in Cubicin RF. Mannitol is listed in the FDA Inactive Ingredients Database (IID) at potency levels higher than those in Daptomycin for Injection and is found in other FDA approved drug products administered by the same route of exposure and duration, at levels higher than those detected in Daptomycin by Injection. There is no concern for use of mannitol at the proposed levels in their drug product. Sorbitol is listed in the FDA Inactive Ingredients Database (IID) at potency levels higher than in Daptomycin for Injection, but not necessarily of sufficient duration to cover the maximum 6-week treatment duration of Daptomycin for injection (for S. aureus blood stream infections, including endocarditis). The Applicant provided additional safety information to justify the level of sorbitol (~ 0.233 mg for the maximum dose expected to be administered to patients of 490 mg/day) in their proposed clinical formulation. This included a detailed review of the published literature that described clinical safety of parenteral nutrition products containing sorbitol approved outside this country at much higher levels and longer durations than in the Applicant's proposed DAPZURA RT for Injection formulation. This published clinical data was reviewed by the DAI clinical review team and was considered reasonable to support the safety of sorbitol in daptomycin for injection. There is no concern for use sorbitol in their drug product.

Two new impurities, (b) (4) were identified (b) (4) in the Applicant's new daptomycin for injection formulation that exceeded the qualification threshold described in ICH Guidances (b) (4) The Applicant conducted a 30-day toxicology study in rats with the LD and the (b) (4) daptomycin (b) (4) to qualify impurities (b) (4) at the proposed specification levels in the final new drug formulation ((b) (4)% for impurities (b) (4) respectively). Overall, both the Applicant's Daptomycin for Injection and the LD Cubicin RF were similarly well tolerated in rats at a clinically relevant, dose level of 20 mg/kg without notable systemic findings. The results of a bone marrow micronucleus assay included in the 30-day toxicology study indicated that Daptomycin impurities (b) (4) were not clastogenic. From a pharmacology/toxicology perspective, the 30-day toxicology study is

considered adequate and impurities (b) (4) are considered qualified up to the Applicant's proposed specified limits.

Two additional impurities detected in Daptomycin for Injection, (b) (4)

The Applicant's proposed acceptance criteria of ≤(b) (4) ppm (b) (4) (equivalent to ~ (b) (4) µg a day in a maximum patient dose of 490 mg) is lower than the levels described in the referenced Master File (b) (4) and is therefore acceptable from a pharmacology/toxicology perspective. For (b) (4) the Applicant originally proposed an acceptance criteria limit of ≤(b) (4) ppm, which was higher than the previously accepted ≤ (b) (4) ppm in the referenced MF (b) (4) Based on the low level of this impurity actually detected in the final drug product, the Applicant agreed with the Agency's recommendation to lower the (b) (4) acceptance criteria to ≤ (b) (4) ppm, to match what was previously described in the referenced MF (b) (4) (≤ (b) (4) ppm, equivalent to (b) (4) µg/day) and this level is therefore acceptable from a pharmacology/toxicology perspective

The DAPZURA RT for injection container closure consists of a (b) (4) 10 mL glass vial and (b) (4) (b) (4) stopper. The applicant conducted an initial leachable products assessment (6-month storage period) to identify potential leachable products originating from the container closure system. Several solvents were identified in the leachables assessment that were well below the permitted daily exposure levels recommended in ICH Guidances. In addition, there were no other leachables detected in the new drug formulation that exceeded the recommended 5 mcg/day safety concern threshold limit for qualification. In a follow-up, longer-term leachable compounds assessment (22-month storage period) submitted late in the review cycle, 13 leachable compounds that exceeded the safety qualification threshold of 5 mcg/day were identified. for which the Applicant conducted a toxicological risk assessment. In the review of the Applicant's toxicology assessment, the review team determined that the Applicant did not provide sufficient safety qualification information for 5 of the identified leachable compounds. In the absence of adequately safety information available for these 5 identified leachable compounds (b) (4) (b) (4) the pharmacology/toxicology review team is unable to provide agreement on the approval of NDA 213645 for DAPZURA RT for injection.

The label for DAPZURA RT for injection complies with the current Physician Labeling Rule (PLR) formatting and there are no recommended changes to any pharmacology/toxicology relevant sections of the labeling.

Referenced NDAs, BLAs, DMFs

NDA 021572 (listed drug Cubicin RF) and MF (b) (4) Daptomycin (API).

Review of Information Included in the NDA

The current 505(b)(2) NDA is for lyophilized DAPZURA RT for Injection 500 mg/vial intended for intravenous use following reconstitution with sterile water for injection (and further dilution with 0.9% sodium chloride for injection, where indicated) submitted by Baxter Healthcare Corporation. Daptomycin for Injection (Cubicin RF, Merck) is FDA approved and available as a lyophilized powder intended for reconstitution with a suitable intravenous solution prior to administration. Baxter's proposed Daptomycin for Injection was developed to be similar to listed drug (LD) CUBICIN RF regarding lyophilized vial storage conditions, in use shelf life, diluent for reconstitution, and pH of the reconstituted solution. Sucrose is used (b) (4) for the LD, while the proposed Baxter product contains mannitol and sorbitol (b) (4) (see formulation Table 1 below).

Table 1. Formulation Comparison

Component	Baxter Proposed Product: Daptomycin for Injection		Reference Product: CUBICIN RF (Daptomycin for Injection)	
	Amount in Container[a]	Concentration upon Reconstitution for Administration	Amount in Container[a]	Concentration upon Reconstitution for Administration
Daptomycin	500 mg	50 mg/mL	500 mg	50 mg/mL
Sorbitol	238 mg	23.8 mg/mL	N/A	N/A
Mannitol	238 mg	23.8 mg/mL	N/A	N/A
Sucrose	N/A	N/A	713 mg	71.3 mg/mL
Sodium Hydroxide	As needed	N/A	As needed	N/A
Hydrochloric Acid	As needed	N/A	N/A	N/A

N/A = Not Applicable

[a] Amount stated in prescribing information.

(Applicant Table 3, Section 3.2.P.1 Description and Composition of the Drug Product).

Comments on Excipients

The excipients mannitol and sorbitol are structurally similar sugar alcohols listed in the FDA Inactive Ingredients Database (IID) at potency levels higher than those in Daptomycin for Injection, but not necessarily of sufficient duration to cover the maximum 6-week treatment duration of Daptomycin for injection (for S. aureus blood stream infections, including endocarditis). The Applicant provided additional safety information to justify the level of sorbitol in their proposed clinical drug formulation.

Mannitol

The Applicant's proposed specification for mannitol in the finished product is 238 mg/vial (Section 3.2.P.2.2) in 500 mg lyophilized DAPZURA RT for Injection vial (or 0.233 mg in the

maximum expected dose in patients of 490 mg) to be reconstituted in 10 mL (b) (4) water. Mannitol is found in other FDA approved drug products administered by the same route of exposure and duration, at levels higher than those detected in DAPZURA RT by injection. There was no concern for use of mannitol at the proposed levels in their drug product.

Sorbitol

The proposed specification in the finished product is 238 mg/vial (Section 3.2.P.2.2) in 500 mg lyophilized DAPZURA RT for Injection vial (or 0.233 mg in the maximum expected dose in patients of 490 mg) to be reconstituted in 10 mL (b) (4) water. Sorbitol is found in other FDA approved drug products administered intravenously at levels higher than those detected in the new DAPZURA RT for Injection, however these products are administered for less than 6 weeks duration (treatment duration for patients with endocarditis/bacteremia). Following a request to the Applicant to provide additional information on the safety of sorbitol (in DARRTS, January 6, 2021), the Applicant provided a review of the clinical safety of parenteral nutrition products containing sorbitol approved outside the US containing this excipient at much higher levels than in the Applicant's proposed DAPZURA RT for Injection formulation. This new information from published sources was reviewed by the DAI clinical review team and was considered reasonable to support the safety of sorbitol at the proposed levels in Daptomycin for Injection administered intravenously for the 6-week clinical duration. There is no concern for use of mannitol at the proposed levels in their drug product.

Comments on Impurities

Two new impurities (b) (4) were identified in the Applicant's new daptomycin for injection formulation that exceeded ICH qualification thresholds (b) (4) (b) (4) The Sponsor conducted a 30-day repeat-dose toxicology study in rats to qualify these impurities.

Impurity (b) (4)

(b) (4)

Impurity (b) (4) was adequately qualified up to the proposed limit in a 30-day repeat dose rat

toxicology study at comparable or greater levels than those detected in the clinical formulation of Daptomycin for Injection at the maximum dose expected to be administered to patients at 490 mg/day.

Impurity (b) (4)

(b) (4)

The Applicant originally proposed a specification limit for daptomycin impurity (b) (4) In a follow-up communication with the FDA, the Applicant agreed with the Agency's recommendation to lower impurity (b) (4) specifications (b) (4) Impurity (b) (4) was adequately qualified up to the proposed limit in a 30-day repeat dose rat toxicology study at comparable levels to those detected in the clinical formulation of Daptomycin for Injection at the maximum dose expected to be administered to patients of 490 mg/day.

Comparative stability testing data in Table 2 indicate that Daptomycin (b) (4) (b) (4) (largest mean values for Cubicin RF at expiry are also provided for reference). These factors were considered by the Applicant when setting the proposed acceptance criteria (AC) of no more than (NMT) (b) (4)% at release and (b) (4)% shelf life for (b) (4) and NMT (b) (4)% at release and (b) (4)% shelf-life (b) (4)

Table 2. Qualification Threshold, Proposed Acceptance Criteria and Comparative Stability Data

Table 2. Chemical Name (Code#)	Qualification Threshold QT (%)[a]	Proposed Acceptance Criteria (AC) %	Largest Mean Value Developmental Stability Units at 25°C for 24 Months (% w/w)[b]	Largest Mean Value Registration Stability Batches at 25°C for 12 Month (% w/w)[c]	Largest Mean Value Registration Stability Batches Intermediate 30°C for 12 Months (% w/w)	Largest Mean Value LD CUBICIN RF at Expiry (% w/w)[d]
(b) (4)						

(Table values taken from Applicant Tables 2 and 3, Section 3.2.P.5.6).

Reviewer Evaluation of Qualification of Impurities (b) (4) in the 30-Day Toxicology Study

Impurities (b) (4) were adequately qualified up to the proposed specified limits in a 30-day repeat dose rat toxicology study at comparable or greater levels than those detected in the clinical formulation of Daptomycin for Injection at the maximum dose expected to be administered to patients of 490 mg/day. Results from a bone marrow micronucleus assay, which was included in the 30-day toxicology study, indicate that Daptomycin impurities (b) (4) (b) (4) are not clastogenic.

Study title/ number: Study Title: 30-Day Intravenous Toxicity Impurity Qualification Study of Daptomycin for Injection in Sprague Dawley Rats with Evaluation of Induction of Micronucleated Erythrocytes in Bone Marrow. Study report number: U-18327.

Sprague Dawley rats were intravenously administered either saline Daptomycin for Injection (20 mg/kg/day) or listed drug Cubicin RL (20 mg/kg/day) once daily for 30 consecutive days. Dose selection was based on a previous non GLP 14-day study in Sprague Dawley rats administered Daptomycin for Injection at a dose level of 20 mg/kg/day that was well tolerated and without overt adverse effects. This dose was also selected to achieve comparable exposures in rat to qualify the safety of impurities (b) (4) (b) (4) in Daptomycin. The exposure level of impurity (b) (4) in the 30-day toxicology study in rats ((b) (4) mg/kg, based on body surface area comparisons) was slightly higher than the level of impurity (b) (4) ((b) (4) mg/kg) in patients receiving the maximum planned dose of 490 mg/day of daptomycin for injection. For impurity (b) (4) the exposure level in the 30-day toxicology study in rats ((b) (4) mg/kg, based on body surface area comparisons) was

comparable to the exposure level of impurity (b) (4) ((b) (4) mg/kg) in patients receiving the maximum planned dose of 490 mg/day of Daptomycin for Injection. Table 3 below shows the parameters considered for human equivalent dose (HED) calculation and dose setting for the 30-day toxicology.

Table 3. Parameters Considered for HED Calculation and 30-Day Toxicology Study Dose Setting

Impurity (Code#)	Animal Dose (mg/kg)	HED[a] (mg/kg)	Impurity in 30-day Rat Study[b] (%)	Impurity Specification In Final Drug Formulation (%)	Impurity Level at Patient MDD of 490 mg (mg/kg)
(b) (4)	20 mg/kg	(b) (4)			
	20 mg/kg				

[a]HED = Animal dose (mg/kg) x percent impurity x (animal weight [kg] / human weight [kg])$^{0.33}$; Animal weight (30-day toxicology study) = 0.3 Kg. Human weight = 60 kg.

[b]Impurities in the 30-day toxicology study (b) (4)

Key findings

- The 30-day toxicology study was considered adequate and the qualification of impurities (b) (4) in Daptomycin at levels comparable to or higher than those expected in patients receiving the maximum planned dose of 490 mg/day of Daptomycin for Injection was acceptable.
- Overall, both Daptomycin for Injection and Cubicin RF were well tolerated in rats at a single dose level of 20 mg/kg without notable systemic findings.
- Daptomycin for Injection- and Cubicin RF-related findings were comparable in incidence and severity and included minimal decreases in white blood cells, fibrinogen levels and serum triglycerides, low incidence cecal enlargement, minimal findings in the kidneys (tubular vacuolation), minimal findings in the lung (perivascular infiltration of inflammatory cells) and marginal changes in organ weights (decreased adrenal, thyroid, parathyroid and pituitary glands, liver, kidney weight and increased spleen weight).

- Minimal axonal degeneration of the sciatic nerve was observed in one animal treated with the Cubicin RF but not with Daptomycin for Injection.
- Epidermal crust formation was observed around the injection site of most rats (including those in the control group) that correlated with microscopic lesions including minimal perivascular fibrosis, mononuclear cell infiltration and thrombus.
- Daptomycin for injection impurities (b) (4) were not clastogenic in the rodent micronucleus assay.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: Yes (21 CFR Part 58).

Methods

Dose and frequency of dosing:	20 mg/kg/day, once daily for 30 days
Route of administration:	IV slow injection given over a 2-minute period via the lateral rat vein (vehicle, test article and listed drug); oral gavage (positive control, cyclophosphamide).
Formulation/Vehicle:	Test article solution prepared by adding 418 Daptomycin for Injection (lyophilized cake) to 10 mL of sterile water and reconstituted to get a 41.8 mg/mL stock solution. 4.8 mL of stock solution were further diluted with sterile saline to obtain a 50 mL volume. The Applicant notes that the that the drug product (b) (4) (b) (4) in the study formulation (Justification of Specifications Section 3.2.P.5.6). The amounts of (b) (4) in the daptomycin test article were (b) (4) % and (b) (4) %, respectively. The listed drug, Cubicin was prepared similarly (500 mg Cubicin + 10 mL sterile water; 4 mL further diluted with sterile saline to a total volume of 50 mL). Solutions were prepared daily and used within 4 hours. Normal saline (0.9% sodium chloride) was used to dose animals in the vehicle group. For the positive control in the micronucleus test a single dose (40 mg/kg) of cyclophosphamide was administered by oral gavage (5 animals/sex/group) in a dose volume

of 10 mg/kg on day 30, 24 hours before sacrifice.

Species/Strain: Rat/ Sprague Dawley.
Number/Sex/Group: 10/sex/group for vehicle, Daptomycin for Injection and Cubicin RF.

Age: 8 weeks old.
Satellite groups/ unique design: None.
Deviation from study protocol affecting interpretation of results: None that had any impact on the outcome of the study.

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	None
Ophthalmoscopy	None
Hematology	Decreased white blood cells (-15-16%) and neutrophils (-35-40%) in males and eosinophils (-15-18%) in males and females treated with either test article or listed drug when compared to vehicle controls. Fibrinogen levels were minimally increased (5-7%) in males treated with either test article of listed drug and slightly decreased (-5%) in females treated with test article. Findings were without correlates of systemic toxicity.
Clinical Chemistry	Triglycerides were similarly decreased in test article (-26%) and listed drug (-37%) treated females.
Urinalysis	None
Gross Pathology	Cecal enlargement in males and females treated with either test article (2-3/10 animals) or listed drug (2-4/10 animals). This finding was without histological correlates.
Organ Weights	Changes in organs weights were observed in some males and females treated with test article or listed drug (5-8% decreases in adrenals, thyroid/parathyroid, liver, pituitary; 8% increase in spleen weight) when compared to vehicle control, however these changes were marginal and without histological correlates.

Histopathology Adequate battery: Yes.	Minimal epithelial vacuolation was observed in the renal cortical tubules of males and females treated with both the test article and listed drug that were comparable in incidence (8-10/10 animals) and severity (minimal). There were no additional histological findings indicative of kidney toxicity (e.g., cellular necrosis, degeneration). This finding is consistent with the kidney being a potential target organ of toxicity for daptomycin drug products, including the LD Cubicin RF. Perivascular infiltration of mixed cells (predominantly polymorphonuclear cells and a few macrophages and lymphocytes), and interstitial infiltration of mononuclear cells (macrophages and lymphocytes) were noted in the lungs of males (4-7/10 animals) and females (6-8/10 females) treated with either test article or listed drug that were comparable in severity (minimal). Similar lung findings were observed in 1/10 males in the control group. Axonal degeneration (minimal) was observed in 1/10 animals treated with the listed drug. Although not observed in animals treated with the test article, this finding is consistent with known nervous system effects (including axonal degeneration) of daptomycin drug products on peripheral nerve including for the listed drug Cubicin RF. There were minimal, low incidence injection site findings (epidermal crust, perivascular fibrosis, mononuclear cell infiltration, thrombus) in some animals across all groups, including those in the control group, and likely associated with the injection procedure.

-: indicates reduction in parameters compared to control.

The clastogenic potential of Daptomycin was also investigated in a bone marrow micronucleus assay included in the 30-day toxicology study. The assay was considered valid because it included the following: adequate bone marrow cell count and scoring approach (minimum count of 500 erythrocytes; minimum of 4000 PCE's sored per animal, positive and negative controls within laboratory historical data ranges), and inclusion of positive control article which induced responses statistically significantly higher when compared to concurrent controls. Daptomycin for injection containing impurities (b) (4) was negative for induction of micronuclei under the conditions tested.

Reviewer comment: Overall, both the test article Daptomycin for Injection and the listed drug Cubicin RF were well tolerated in the 30-day repeat dose toxicology study in the rat. The few test article- and listed drug-related findings were not associated with overt organ or systemic toxicity and were comparable in severity and incidence, indicating a similar toxicological profile between daptomycin by injection and Cubicin RF. The Applicant did not provide a comparative TK analysis between the listed drug and the new drug containing mannitol and sorbitol, however, the addition of these excipients (b) (4) is not likely to impact ADME, and therefore is of little concern. Histopathological evaluation revealed microscopic findings in the kidney which consisted of minimal epithelial vacuolation in the renal cortical

tubules of animals treated with both the test article and listed drug that were comparable in incidence and severity. It is noteworthy that minimal axonal degeneration was observed in one animal treated with the listed drug but not with daptomycin for injection and this finding is consistent with known nervous system effects (including axonal degeneration) of daptomycin drug products on peripheral nerve including the listed drug Cubicin RF.

Other Genetic Toxicity Studies

Study Report Titles:

- Special Report Toxicology Assessment BXU538454 (Q)SAR Analysis Predicting the Mutagenicity Potential of Impurity (b) (4) in Daptomycin for Injection.
- Special Report Toxicology Assessment BXU545058 – Proposed Specification Limit for Impurity (b) (4) in Daptomycin for Injection.

The Applicant evaluated the mutagenic potential of daptomycin impurities (b) (4) (Report BXU538454) and (b) (4) (Report BXU545058) by conducting in silico analysis predictive of structural alerts that may indicate mutagenic potential in a bacterial in vitro assay (Ames). As per M7(R1) recommendations, the analysis included both a statistical-based model (Sarah Nexus 3.0.0) and an expert rule-based model (Derek Nexus 6.0.1.) The analysis results indicated that impurities (b) (4) were predicted negative for in vitro bacterial mutagenicity. CDER's Computational Toxicology Service (CTCS)[1] reviewed the Applicant's in silico analysis and agreed with the Applicant's conclusions (see Table with comparative prediction reports below). Therefore, there are no mutagenicity concerns for the identified impurities (b) (4) in Daptomycin for Injection.

[1] Division of Applied Regulatory Science within CDER Office of Clinical Pharmacology, Office of Translational Sciences.

No.	Chemical Structure and Name	Sponsor's Bacterial Mutagenicity Overall Prediction[1]	Agency's Bacterial Mutagenicity Expert Prediction[1]
1	(b) (4)	-	-
2		-	-

- = negative

Additional impurities identified in Daptomycin for Injection included (b) (4)

(b) (4)

For (b) (4) the Applicant proposed an acceptance criteria limit ≤ (b) (4) ppm, which is lower than the level previously described in the referenced MF (b) (4) (≤ (b) (4) ppm, equivalent to (b) (4) µg/day), and is therefore acceptable from a pharmacology/toxicology perspective.

(b) (4)

The Applicant originally proposed an acceptance criteria limit for (b) (4) at ≤ (b) (4) ppm, which was a higher than the previously described ≤ (b) (4) ppm in the referenced MF (b) (4) Based on the low level of this impurity actually detected in the final drug product, the Applicant later agreed with the Agency's recommendation to lower the (b) (4) acceptance criteria to ≤ (b) (4) ppm, to match what was previously described in referenced MF (b) (4) (≤ (b) (4) ppm, equivalent to (b) (4) µg/day) and this level is therefore acceptable from a pharmacology/toxicology perspective.

Comments on Leachables

The Applicant conducted a leachables assessment to identify leachables originating from the Container Closure System ((b) (4) 10 mL Glass Vial and (b) (4) stopper). One batch of Daptomycin for injection stored at 40°C/75% RH for 6 months, was reconstituted using 10mL of water per the instructions for IV administration, left inverted for 24 hours at room temperature, followed by a 6-months storage period and analyzed by a Gas Chromatograph coupled to Mass Spectrometer and Flame Ionization Detectors (GCMS/FID). Only (b) (4) were detected as leachables in the drug product at levels equivalent to (b) (4) mg/day, (b) (4) mg/day and (b) (4) mg/day, respectively. The Applicant compared the maximum detected amounts of the 3 solvents to the permitted daily exposures (PDE) recommended in ICH Q3C Guidance to obtain margins of exposure (See Applicant Table 4 below). Overall, the potential maximum daily exposure to (b) (4) ((b) (4) mg/day, respectively) were well below the PDE values ((b) (4) mg/day respectively) and do not appear to raise safety concerns. There were no other leachables detected in the new drug formulation that exceeded the FDA recommended 5 mcg/day safety concern threshold (SCT) limit.

Table 4. Summary of Toxicological Risk Associated with Volatile Leachables in Daptomycin for Injection

Leachable	CAS No.	Permitted Daily Exposure (PDE)[a] (mg/day)	Maximum Detected Amount (mg/day)	Margin of Safety[b]
(b) (4)				

[a] Permitted Daily Exposure values extracted from USP<467> Residual Solvents

[b] Margin of safety calculated as follows: PDE/Maximum Amount Detected

(Applicant Table 2, quality information request August 28, 2020).

In response to a FDA information request (March 21, 2021) communicated to the Sponsor requesting longer term stability testing data, the Sponsor provided a longer term (22-month storage period) assessment of leachable compounds (Study Report BXU562758) where several leachables (13 total) were identified (See Table 5 below).

Table 5. Leachables in Daptomycin; 500 mg *(after reconstitution with 10mL of Water For Injection; WFI)*

Name of Leachable	Detected in Daptomycin		22 Months Amount Detected[c] (µg/mL)
	6 Months[a] (40°C/75%RH)	22 Months[b] (25°C/60%RH)	
(b) (4)			

(Table 1, Study Report BXU562758).

For the following leachable compounds, the Applicant provided sufficient safety qualification data. Three identified solvents (b) (4) ((b) (4) ug in 490 mg maximum patient dose, respectively) were below FDA recommended daily exposures (PDEs of (b) (4) mg/day, respectively) in ICH Q3C Guidance. For (b) (4) (b) (4) the Applicant referenced an FDA safety assessment conducted by the Office of Medical Devices including a calculated tolerable intake of (b) (4) ug/kg/day, which is higher than the (b) (4) ug in the maximum patient dose of daptomycin (490 mg). For (b) (4) the Applicant proposed an acceptable intake of (b) (4) mcg/kg/day based on values included in a draft US EPA Integrated Risk Information System (IRIS) and the use of a conservative adult weight of 50 kg resulting in a (b) (4)-fold safety margin. Following an independent evaluation of the primary data used in the derivation of the reference dose in IRIS and its associated assumptions, we considered the Applicant's evaluation reasonable. Therefore, the levels of these specific

leachable compounds in daptomycin for injection are acceptable from a pharmacology/toxicology perspective.

For 5 leachables (See Table 6 below) that exceeded the FDA's recommended total intake limit of 5 mcg/day the applicant did not provide sufficient information to support the safety qualification of those leachables. The data provided by the Applicant primarily consisted of toxicological risk assessments based on data from either toxicological information websites (primarily (b) (4) toxicological database) or references of unpublished information. Since the information provided was not acceptable (as it was based on third-party summaries or proprietary study reports not available to the Applicant or FDA for independent review), an IR was issued (March 19, 2021) requesting the Sponsor to provide the source of data used for their leachable compounds risk assessments necessary for the conduct of an independent toxicological assessment by the Agency (e.g., study reports, published data). In the Applicant's response to an information request (received March 31, 2021), similar summary data was provided by the Applicant, including some additional hyperlinks to public databases (b) (4) with toxicological summaries and conclusions based primarily on unpublished data (i.e., proprietary information from Industry not available to the Applicant or FDA). In the absence of the actual study reports or published information the summary reviews are based upon, we are unable to agree that these leachables were adequately assessed for safety. Therefore, these 5 leachable compounds are not considered adequately qualified from a pharmacology/toxicology perspective.

Table 6. Information from 22-month leachable analysis (based on information in Study Report BXU562758)

Leachable	Detected		Amount detected in 22-month analysis (µg/490 mg max human dose)	Information provided
	6-month analysis	22-month analysis		
(b) (4)				

(Reviewer Table, information taken from Study Report BXU562758).

Six leachable compounds were further evaluated for their mutagenic potential by CDER's Computational Toxicology Service (CTCS)[2] using in predictive silico analysis. As per M7(R1) recommendations, the analysis included both a statistical-based model (Sarah Nexus 3.0.0) and an expert rule-based model (Derek Nexus 6.0.1.) The analysis results indicated that the following leachable compounds, (b) (4) (b) (4) were predicted negative for in vitro bacterial mutagenicity (see Table below including summary expert prediction reports). Therefore, there are no mutagenicity concerns for these 6 leachable compounds in Daptomycin for Injection.

No.	Chemical Name	Structure	Bacterial Mutagenicity Predictions[2]				Comments
			DX	LMA	CU	Overall Expert	
1	(b) (4)		-	N	N	-	(b) (4)
2			-	N	N	-	
3			-	N	N	-	
4			-	-	-	-	
5			-	N	N	-	
6			-	-	-	-	

[2] - = negative; N = experimentally negative in model training set

[2] Division of Applied Regulatory Science within CDER Office of Clinical Pharmacology, Office of Translational Sciences.

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/s/

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