CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213645Orig1s000

SUMMARY REVIEW

NDA Summary Review

NDA #	213645
Applicant	Baxter Healthcare
Date of Resubmission	July 30, 2021
PDUFA Goal Date	January 30, 2022
Proprietary Name / Established (USAN) names	DAPZURA RT (daptomycin for injection)
Dosage forms/Strength	Lyophilized powder for injection, 500 mg/vial
Proposed Indication(s)	• Complicated skin and skin structure infections (cSSSI) in adult and pediatric patients (1 to 17 years of age). • *Staphylococcus aureus* bloodstream infections (bacteremia), in adult patients including those with right-sided infective endocarditis. • *Staphylococcus aureus* bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age).
Regulatory Action:	Approval

1. Background

Daptomycin is a cyclic lipopeptide antibacterial drug. It is used in the treatment of infections caused by aerobic gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin includes gram-positive bacteria including *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates). Its mechanism of action is through binding to components of the cell membrane of susceptible organisms causing a rapid depolarization of membrane potential. This loss of membrane potential inhibits DNA, RNA, and protein synthesis, which results in bacterial cell death.

The Applicant, Baxter Healthcare, originally submitted NDA 213645 on June 30, 2020, as a 505(b)(2) application and received a Complete Response (CR) letter on April 29, 2021, due to an inadequate safety qualification of leachables detected in a leachables assessment of the proposed drug product. Please see the Multidisciplinary NDA Summary Review signed into DARRTS on April 29, 2021, for additional details related to the original submission

To note, the Applicant states that Dapzura RT contains the same active ingredient, strength, dosage form, preparation, and route of administration as the Listed Drug (LD), CUBICIN, with differences in excipients. The proposed new formulation of daptomycin for injection contains mannitol and sorbitol, as opposed to sucrose, which is present in the LD. No clinical studies have been conducted by the Applicant.

2. Current Submission

The Applicant, Baxter Healthcare, resubmitted this NDA on July 30, 2021, in response to the Agency's CR action. The proposed indications and dosing regimens are the same as in the original NDA.

In this submission, the Applicant provided the following: (1) a Quality Information Amendment in Response to CR Letter; (2) Baxter's Response to Type A Meeting Preliminary Comments (Updated Toxicology Risk Assessment for Leachables); (3) Resubmission of Request for Proprietary Name Review; (4) Clinical Safety Update Report; (5) Revised Container and Carton Labeling; and (6) Revised Draft Labeling Text.

Product Quality/Chemistry, Manufacturing and Controls (CMC):

From the Product Quality perspective, comprehensive CMC information for the proposed drug substance (daptomycin) and the drug product (daptomycin for injection) was provided in the original NDA and no specific product quality related deficiencies were identified. However, the qualification information submitted for several identified leachables, as assessed by the Pharmacology/Toxicology team, was found inadequate. Therefore, this NDA was not recommended for approval by the OPQ review team in the first review cycle (please refer to the OPQ review, dated April 26, 2021, in DARRTS for additional details). The NDA resubmission provides information to address the qualification of leachables, which was found adequate by the Pharmacology/Toxicology team, and does not include any changes or updates to the CMC sections. All manufacturing and testing facilities are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on November 9, 2021. Therefore, this NDA is recommended for approval by the OPQ team (refer to the OPQ review # 2, dated December 17, 2021, in DARRTS).

Pharmacology/Toxicology:

The NDA, originally submitted on June 30, 2020, received a CR on April 29, 2021, because the Applicant did not provide sufficient safety qualification data for five leachable compounds (b) (4) identified in a leachables assessment with their drug product (b) (4) (b) (4) While there were no mutagenicity concerns for any of the identified leachables, the Applicant's safety qualification approach for leachable compounds exceeding the safety concern threshold (SCT) of 5 mcg/day did not provide adequate information to characterize the general toxicity of the identified leachables (see Pharmacology/Toxicology review of the original NDA in DARRTS from April 28, 2021, for additional details). In response to FDA's CR Letter, the Applicant provided sufficient nonclinical information to address the deficiencies identified in toxicological risk assessments for the 5 unqualified leachables (b) (4) (b) (4) These data included primary sources of toxicological information and bioavailability data to account for route-to-route extrapolations for studies conducted by routes of exposure other than the intended intravenous administration for Dapzura. For leachables with limited toxicological data, the Applicant provided primary toxicological information for acceptable surrogate compounds. Based on review of the toxicological studies, the No Observable Adverse Effect Levels (NOAELs) or Lowest Observed Adverse Effect Levels (LOAELs), and Permissible Daily Exposure (PDE) levels determined for the 5

leachables and margins to the maximum potential exposure to patients administered Dapzura by the intravenous route were calculated in accordance with methods described in ICH Guidance Q3C(R8)[1] (see Table 1 below).

Upon review of the submitted information, the Pharmacology/Toxicology review team has determined that the submitted toxicological assessments are considered adequate and that the calculated PDEs have reasonable exposure margins to the maximum potential leachable exposure to patients administered Dapzura RT for injection. From a Pharmacology/Toxicology perspective, the leachables in Dapzura for injection (b) (4) are considered adequately qualified. Refer to the Pharmacology/Toxicology review for this NDA resubmission signed into DAARTS on December 17, 2021, for additional information.

Table 1. Summary of Maximum Leachable Exposures and Exposure Margins 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 (µg/day) calculated using the assumption of a 70 kg human for comparability to Applicant approach; PDE and exposure margins calculated according to ICH Guidance Q3C(R8).

Clinical:

In the original NDA submission, the following issues were discussed in detail: (i) the

[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.

(b) (4)

safety of the excipients mannitol and sorbitol, and (ii) adding a contraindication and warning in the labeling for patients with known or suspected Hereditary Fructose Intolerance (HFI). Please see the Multidisciplinary NDA Summary Review signed into DARRTS on April 29, 2021, for details related to the original submission.

In the resubmission, the Applicant provided a safety update document and revised labeling.

I. Safety Update
The safety update document was based on the Applicant's review of literature published between September 2020 and June 2021. No new safety information was identified. Most of the literature discussed known adverse events associated with daptomycin including elevated creatinine phosphokinase levels, abnormal liver function tests, diarrhea, myalgia, rash, rhabdomyolysis, and eosinophilic pneumonia. Several publications described the use of higher than approved doses of daptomycin in adults.

II. Labeling
As described in the review of the original submission, Dapzura RT contains sorbitol, which has a risk of metabolic crisis in patients with known or suspected HFI. The Applicant added a contraindication and warning to the labeling submitted in the resubmission (Section 4, 5.11, and 8.4). Also, warnings regarding drug reaction with eosinophilia and systemic symptoms (DRESS) and tubulointerstitial nephritis (TIN) were added to sections 5.4 and 5.5, respectively, and the warning related to the development of drug-resistant bacteria was modified in section 5.13 based on the LD. Additionally, toxic epidermal necrolysis (TEN) was added to the skin and subcutaneous tissue disorders system organ class subsection in section 6.2, Post-marketing Experience; and section 17, the Patient Counseling Information, was revised. The latter two revisions were the result of a labeling update to the LD which occurred on October 26, 2021.

3. Regulatory Action

This New Drug Application (NDA 213645) for Dapzura RT (Daptomycin for Injection), 500 mg/vial, will receive an approval action.

Reviewers:
Clinical: Jae Ho Hong, M.D.
Acting Clinical Team Leader: Hiwot Hiruy, M.D., Ph.D.
Nonclinical Team Leader and Cross-Discipline Team Leader: Terry J. Miller, Ph.D.
Division Director: Peter Kim, M.D., M.S.

Signatures: *{See appended electronic signature page}*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JACQUELYN C ROSENBERGER
01/18/2022 02:45:04 PM

JAE H HONG
01/18/2022 03:54:27 PM

MUKILAN NATARAJAN
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Signing as proxy for Hiwot Hiruy (team leader)

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NDA Summary Review

Date	April 24, 2021
NDA #	213645
Applicant	Baxter Healthcare
Date of Submission	June, 30, 2020
PDUFA Goal Date	April 30, 2021
Proprietary Name / Established (USAN) names	DAPZURA RT (Daptomycin for Injection)
Dosage forms/Strength	Lyophilized powder for injection in a single-dose vial, 500 mg
Proposed Indication(s)	• Complicated skin and skin structure infections (cSSSI) in adult and pediatric (1 to 17 years of age) patients. • *Staphylococcus aureus* bloodstream infections (bacteremia), in adult patients including those with right-sided infective endocarditis. • *Staphylococcus aureus* bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age).
Regulatory Action:	Complete Response

1. Background

Daptomycin is a cyclic lipopeptide antibacterial drug. It is used in the treatment of infections caused by aerobic Gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin includes Gram-positive bacteria including *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates). Its mechanism of action is through binding to components of the cell membrane of susceptible organisms and causes rapid depolarization, inhibiting intracellular synthesis of DNA, RNA, and protein.

On October 5, 2018, the Applicant submitted a request for a pre-IND meeting to discuss the development program for their proposed daptomycin for injection. The Division granted a written response only meeting and responses were sent on November 30, 2018.

2. Current Submission

The Applicant, Baxter Healthcare, submitted this 505(b)(2) New Drug Application (NDA) for Dapzura RT that relies on FDA's finding of safety and effectiveness for the listed drug (LD), Cubicin RF (daptomycin for injection) lyophilized powder 500 mg/vial, NDA 021572, held by Cubist Pharmaceuticals LLC. The Applicant states that Dapzura RT contains the same active ingredient, strength, dosage form, preparation and route of administration as the LD, with differences in excipients. The proposed new formulation of daptomycin for injection contains mannitol and sorbitol, as opposed to sucrose which is present in the LD. No clinical studies have been conducted by the Applicant.

From the Product Quality perspective, comprehensive chemistry, manufacturing and controls (CMC) information for the proposed drug substance (daptomycin) and the drug product (daptomycin for injection) was provided in the NDA. The overall CMC information, including information submitted for the manufacturing and testing facilities, was found acceptable by the OPQ review team, and no specific Product Quality related deficiencies were identified. However, the qualification information submitted for several identified leachabes (as part of the extractable/leachable assessment for the drug product container closure system), and as further evaluated by the Pharmacology/Toxicology team, was found inadequate. Therefore, this NDA is not recommended for approval by the OPQ review team at this time (please refer to the OPQ review, dated April 26, 2021, in DARRTS for additional details).

From a Pharmacology/Toxicology perspective, the Applicant has not provided sufficient safety qualification data for five leachable compounds (b) (4) (b) (4) identified in a leachables assessment with their drug product. While there are no mutagenicity concerns for any of the identified leachables, the Applicant's safety qualification approach for leachable compounds exceeding the threshold of 5 mcg/day does not provide adequate information to characterize the general toxicity of the identified leachables. Please refer to the Pharmacology/Toxicology review in DARRTS on 4/28/21 for additional details.

The clinical safety review and evaluation of the literature and FAERS database have not identified any new potential safety signals for daptomycin for injection.

Dapzura RT contains the excipients sorbitol and mannitol in place of sucrose contained in the RLD. The amounts of mannitol and sorbitol in Dapzura RT are within the Inactive Ingredient Database (IID) limits for the intended route of administration. The amounts of mannitol and sorbitol proposed in Dapzura RT are less or similar with the maximum daily intake (MDI) and maximum infusion rate for other approved drugs. Since the maximum treatment duration for Dapzura RT is 6 weeks, drugs containing mannitol and/or sorbitol that are administered for a similar duration were reviewed. The amounts of mannitol associated with administration of Vibativ and Eraxis are greater than that with Dapzura RT based on MDI and maximum intake per treatment course. No safety issues have been identified related to the mannitol exposure from these products. Gammaplex and Neupogen contain sorbitol as an excipient and depending on the indication, can be administered for a prolonged duration in adults and pediatric patients. The amount of sorbitol exposure with Gammaplex and Neupogen may exceed that with Dapzura RT for a similar duration of treatment. Published studies of parenteral nutrition products containing sorbitol previously marketed outside the U.S. showed that the amount of sorbitol contained in Dapzura RT is less than that in the parenteral nutrition products. The adverse events noted in the literature associated with sorbitol occurred in patients who received much higher doses and over more rapid infusion rates than would be administed during a treatment course of

Dapzura RT. Therefore, the amount of sorbitol in Dazpura RT is acceptable for adult and pediatric patients. Please refer to the Appendix for additional details regarding the review of the MDI and maximum infusion rates for mannitol and sorbitol Dapzura RT versus other approved products.

As noted, Dapzura RT contains sorbitol as an inactive ingredient. Therefore, a Contraindication and Warning are warranted in patients with known or suspected HFI for the following reasons:

(1) Administration of intravenous sorbitol could cause a metabolic crisis in patients with HFI manifested by life-threatening adverse reactions such as hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure.
(2) A metabolic crisis related to sorbitol in addition to underlying sepsis is highly likely to be associated with increased morbidity/mortality in patients with HFI.
(3) The minimum amount of sorbitol at which serious adverse reactions may occur in patients with HFI is not known and intravenous administration should be avoided.
(4) There are other daptomycin products that do not contain sorbitol.

Because a diagnosis of HFI may not yet be established in pediatric patients, a history of HFI symptoms (nausea, vomiting, abdominal pain) with sorbitol/fructose/sucrose exposure should be obtained prior to administration of Dapzura RT.

The clinical reviewer recommends revisions to sections 4, 5 and subsection 8.4 of the proposed labeling similar to the text found in the ERAXIS labelling.

This issue and the proposed labeling were discussed with the Division of Rare Diseases and Medical Genetics (DRDMG). DRDMG concurred with the team's assessment and labeling recommendations. Of note, the LD, Cubicin RF (daptomycin for injection), contains sucrose as an excipient. The team discussed whether the sucrose in the LD could trigger a metabolic crisis in HFI patients. After further consultation with DRDMG who also discussed the issue with a metabolic expert in carbohydrate metabolism, it was determined that there is no evidence that IV sucrose would pose a significant risk for HFI since sucrose is only broken down to fructose and glucose within the GI tract by sucrase.

3. Regulatory Action

New Drug Application (NDA 213645) for Daptomycin Injection, 500 mg/vial, will receive a complete response (CR) action.

The following nonclinical deficiency comment will be included in the CR letter:

"You have not provided adequate safety information to support the qualification of the following 5 leachables (b) (4) (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."

The following comment regarding information needed to resolve the deficiency will also be included in the CR letter:

"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."

4. References

1. Gaughan S, Ayres L, Baker PR II. Hereditary Fructose Intolerance. 2015 Dec 17 [Updated 2021 Feb 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK333439/

2. Yasawy MI, Folsch UR, Schmidt WE, Schwend M. Adult hereditary fructose intolerance. World J Gastroenterol. 2009 May 21;15(19):2412-3. doi: 10.3748/wjg.15.2412. PMID: 19452588; PMCID: PMC2684612.

3. Burmeister LA, Valdivia T, Nuttall FQ. Adult hereditary fructose intolerance. Arch Intern Med. 1991 Apr;151(4):773-6. PMID: 2012463.

4. Cox TM. Aldolase B and fructose intolerance. FASEB J. 1994 Jan;8(1):62-71. doi: 10.1096/fasebj.8.1.8299892. PMID: 8299892.

5. Ali M, Rellos P, Cox TM. Hereditary fructose intolerance. J Med Genet. 1998 May;35(5):353-65. doi: 10.1136/jmg.35.5.353. PMID: 9610797; PMCID: PMC1051308.

6. Woods HF, Alberti KG. Dangers of intravenous fructose. Lancet. 1972 Dec 23;2(7791):1354-7. doi: 10.1016/s0140-6736(72)92791-2. PMID: 4118217.

7. Cox TM. Iatrogenic deaths in hereditary fructose intolerance. Arch Dis Child. 1993 Oct;69(4):413-5. doi: 10.1136/adc.69.4.413. PMID: 8259868; PMCID: PMC1029544.

8. Schulte MJ, Lenz W. Fatal sorbitol infusion in patient with fructose-sorbitol intolerance. Lancet. 1977 Jul 23;2(8030):188. doi: 10.1016/s0140-6736(77)90197-0. PMID: 69795

9. Chérin P, Cabane J. Relevant criteria for selecting an intravenous immunoglobulin preparation for clinical use. BioDrugs. 2010 Aug 1;24(4):211-23. doi: 10.2165/11537660-000000000-00000. PMID: 20623988.

10. Ali M, Rosien U, Cox TM. DNA diagnosis of fatal fructose intolerance from archival tissue. Q J Med. 1993 Jan;86(1):25-30. PMID: 8438046.

5. Appendix

As noted above, Dapzura RT contains 238 mg of sorbitol and 238 mg of mannitol as excipients (per (b) (4) vial) in place of the sucrose excipient found in the LD (Table 1). Dapzura RT also contains sodium hydroxide and/or hydrochloric acid as pH adjusters.

Table 1. Comparison of Proposed Product and RLD (Cubicin RF)

Component	Baxter Proposed Product: Daptomycin for Injection			Reference Product: CUBICIN RF (Daptomycin) for Injection		
	Amount in Container[a]	Concentration upon Reconstitution for Administration	Concentration upon Reconstitution & Dilution[b]	Amount in Container[a]	Concentration upon Reconstitution for Administration	Concentration upon Reconstitution & Dilution[b]
Daptomycin	500 mg	50 mg/mL	7.1 mg/mL	500 mg	50 mg/mL	7.1 mg/mL
Sorbitol	238 mg	23.8 mg/mL	3.4 mg/mL	N/A	N/A	N/A
Mannitol	238 mg	23.8 mg/mL	3.4 mg/mL	N/A	N/A	N/A
Sucrose	N/A	N/A	N/A	713 mg	71.3 mg/mL	10.2 mg/mL
Sodium Hydroxide	As needed	N/A	N/A	As needed	N/A	N/A
Hydrochloric Acid	As needed	N/A	N/A	N/A	N/A	N/A

N/A = Not Applicable

[a] Amount stated in prescribing information.

[b] Per the prescribing information, the appropriate volume of the reconstituted daptomycin product (concentration of 50 mg/mL) should be further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection. The concentration listed assumes 10 mL (500 mg) of reconstituted solution are added to a 50 mL IV infusion bag of 0.9% sodium chloride injection. A 50 mL IV bag contains approximately 60 mL of 0.9% sodium chloride injection; therefore, the total volume in the admixed bag would be approximately 70 mL.

Above table was obtained from Table 3 of special-report-bxu551373.pdf provided by the Applicant (SDN 1)

Mannitol and sorbitol are inactive ingredients in other drug products. (b) (4) [redacted]

The amounts of mannitol and sorbitol in Dapzura RT are within clinically acceptable intake limits for the intended route of administration based on the Inactive Ingredient Database (IID), i.e., 2000 mg and 1.04%w/v, respectively. The Applicant submitted a table comparing Dapzura RT to other FDA-approved products with regard to the maximum daily intake (MDI) and maximum infusion rate for mannitol and sorbitol (Table 2). The amounts of mannitol and sorbitol in Dapzura RT are less than or compatible with the MDI and maximum infusion rates for other approved drugs.

Table 2. Maximum Daily Intake (MDI) of Mannitol and Sorbitol in Daptomycin for Injection Compared to Other FDA-Approved Products

Drug Product	Amount of Sorbitol per Dosage Form	Amount of Mannitol per Dosage Form	MDI of Sorbitol (based on 70 kg adult patient)	MDI of Mannitol (based on 70 kg adult patient)	Max infusion rate of product	Max Sorbitol infusion rate	Max Mannitol infusion rate
Baxter Daptomycin for Injection	238 mg / 10 mL Vial	238 mg / 10 mL Vial	233 mg [a]	233 mg [a]	Total dose infused over 2 min (6 mg/kg/2 min = 3 mg/kg/min)	1.43 mg/kg/min[b]	1.43 mg/kg/min[b]
Flebogamma DIF injection, solution (b) (4)	5,000 mg / 100 mL Vial	None	42,000 mg [c]	None	5 mg/kg/min [d]	5 mg/kg/min [e]	N/A
Argatroban injection, solution (NDA 020883)	750 mg / 2.5 mL Vial	None	3024 mg [f]	None	0.14[g] mg/kg/min	0.42[h] mg/kg/min	N/A
CARDENE I.V. Premixed Injection in 0.83% Sodium Chloride (NDA 019734)	768 mg / 200 mL	None	1612.8 mg[i]	None	15 mg/hr = 3.57 mcg/kg/min[j]	0.069 mg/kg/min[k]	N/A
OSMITROL (Mannitol injection), (NDA 013684)	None	100 g / 500 mL	None	140000 mg[l]	140 g over 30 min = 66.7 mg/kg/min[m]	N/A	66.7 mg/kg/min[m]
OFIRMEV (acetaminophen) Injection (NDA 022450)	None	38.5 mg/mL	None	15,400 mg[n]	1000 mg over 15 min = 0.95 mg/kg/min[o]	N/A	3.66 mg/kg/min[p]
GEMZAR (gemcitabine hydrochloride) injection, powder, lyophilized for solution (1 g/vial) (NDA 020509)	None	1000 mg/vial	None	2250 mg[q]	2250 mg over 30 min = 1.07 mg/kg/min[r]	N/A	1.07 mg/kg/min[s]

MDI: Maximum Daily Intake

a. Maximum daily dose of daptomycin = 490 mg (7 mg/kg x 70 kg). 490 mg/500 mg x 238 mg = 233 mg
b. Maximum infusion rate = 238 mg/500 mg x 3 mg/kg/min = 1.43 mg/kg/min
c. Maximum daily intake of sorbitol = (42000 mg Flebogamma/day ÷ 50 mg Flebogamma/ mL) x (5000 mg sorbitol/100 mL) = 42000 mg sorbitol/day
d. 5 mg/kg/min
Reference to labeling: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2cf22c72-64ac-45be-b7c6-d20340730096
e. Maximum infusion rate of sorbitol = 5 mg/kg/min Flebogamma x 50 mg/mL sorbitol ÷ 50 mg/mL Flebogamma = 5 mg/kg/min sorbitol
f. Maximum daily intake of sorbitol = (1008 mg argatroban/day ÷ 100 mg argatroban/ mL) x (300 mg sorbitol/mL) = 3024 mg sorbitol/day
g. 350 mcg/kg/3 min bolus + 40 mcg/kg/min = 141.7 mcg/kg/min
Reference to labeling: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020883s019lbl.pdf
h. Maximum infusion rate of sorbitol = 0.14 mg/kg/min argatroban x 300 mg/mL sorbitol ÷ 100 mg/mL argatroban = 0.42 mg/kg/min sorbitol
i. Maximum daily intake of sorbitol = (84 mg nicardipine/day ÷ 40 mg nicardibine/200 mL) x (768 mg sorbitol/200 mL) = 1612.8 mg sorbitol/day
j. 15 mg/h ÷ 70kg ÷ 60 min/h = 3.57 mcg/kg/min
Reference to labeling: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0d58f812-37bf-439f-b3f2-c31f8eefe22e
k. Maximum infusion rate of sorbitol = 0.00357 mg/kg/min nicardipine x 768 mg/200 mL sorbitol ÷ 40 mg/200 mL nicardipine = 0.069 mg/kg/min sorbitol
l. Maximum daily intake of mannitol = 2 g/kg x 70 kg = 140000 mg
m. Maximum infusion rate of mannitol = 2000 mg/kg ÷ 30 min = 66.7 mg/kg/min
Reference to labeling: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0d914965-7001-45cb-ba51-d7c5964b05bc
n. Maximum daily intake of mannitol = (4000 mg acetaminophen/day ÷ 10 mg acetaminophen/ mL) x (3850 mg mannitol/100 mL) = 15400 mg mannitol/day
o. 1000 mg ÷ 70 kg ÷ 15 min = 0.95 mg/kg/min
Reference to labeling: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022450lbl.pdf
p. Maximum infusion rate of mannitol = 0.95 mg/kg/min acetaminophen x 38.5 mg/mL mannitol ÷ 10 mg/mL acetaminophen = 3.66 mg/kg/min mannitol
q. Maximum daily intake of mannitol = (2250 mg gemcitabine/day ÷ 1000 mg gemcitabine/vial x 1000 mg mannitol/vial = 2250 mg mannitol
r. 2250 mg ÷ 70 kg ÷ 30 min = 1.07 mg/kg/min
Reference to labeling: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9dc35c59-f4f3-43b4-8251-0cf5c06cdc80
s. Maximum infusion rate of mannitol = 1.07 mg/kg/min gemcitabine x 1000 mg mannitol/vial ÷ 1000 mg gemcitabine/vial = 1.07 mg/kg/min mannitol

Above table was obtained from Table 16 of special-report-bxu551373.pdf (SDN 1)

However, Dapzura RT could be administered for a maximum duration for 6 weeks for the treatment of patients with *Staphylococcus aureus* bloodstream infections (bacteremia) in adult and pediatric patients down to 1 year of age. None of the drugs listed in Table 2 are administered for durations of up to 6 weeks.

Therefore, we requested that the Applicant provide additional information on drugs that contain mannitol and/or sorbitol that are administered for 6 weeks or longer. The Applicant provided additional information (SDN 9; submitted 12/3/2020).

Table 3. Maximum Possible Excipient Intake following Administration of Dapzura RT

Inactive Ingredient	Excipient Amount per 10 mL Vial	Maximum Daily Intake (MDI) of Inactive Ingredient[a]	Maximum Intake per Treatment Course[b]
Mannitol	238 mg/vial	233 mg/day	9786 mg
Sorbitol	238 mg/vial	233 mg/day	9786 mg

[a] The maximum daily intake of the inactive ingredient is based on the maximum daily dose of Daptomycin for Injection of 490 mg [MDI of Inactive Ingredient = (490 mg daptomycin/day ÷ 500 mg daptomycin/vial) x 238 mg (sorbitol and mannitol)/vial= 233 mg/day (sorbitol and mannitol)].

[b] Maximum possible intake is based on the maximum daily intake of sorbitol and mannitol (233 mg/day) multiplied by the maximum possible duration of treatment episode (i.e. 6 weeks = 42 days) = 9786 mg

Table was obtained from page 8 of Quality Information Amendment in Response to IR Comments Received on 2020Nov24.pdf (SDN 9)

A. Mannitol for 6 weeks

Vibativ (telavancin hydrochloride) injection, powder, lyophilized, for solution and Eraxis (anidulafungin) injection, powder, lyophilized, for solution were presented as examples of FDA approved drugs with mannitol. Vibativ is indicated for the treatment of adult patients with complicated skin and skin structure infections or hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible isolates of *Staphylococcus aureus*. Even though the duration of treatment for the approved indication is less or equal to 3 weeks, Vibativ has been studied and has been used for the treatment of *Staphylococcus aureus* bacteremia, osteomyelitis, prosthetic joint infections, and endocarditis for durations of 6 weeks.

Eraxis is indicated for the treatment of fungal infections including, candidemia, other forms of Candida infections (intra-abdominal abscess, and peritonitis), and esophageal candidiasis. Candidemia and other forms of Candida infections are treated for at least 14 days after the last positive culture and are commonly treated for up to 6 weeks. For Candidemia and other forms of Candida infections, Eraxis is indicated for adults and pediatric patients of 1 month of age and older. As shown in Table 4, the MDI of mannitol in Vibativ and Eraxis are 875 mg/day and 1000 mg/day, respectively. These are greater than the MDI of Dapzura RT which is 233 mg/day. Also, the maximum intake per treatment course of Vibativ (3 weeks) and Eraxis (6 weeks) are 18,375 mg and 21,500 mg, respectively, which are greater than the 9,786 mg maximum intake for a 6-week treatment course of Dapzura RT. No safety issues have been identified related to the mannitol exposure from these products.

Table 4. Maximum Possible Intake of Mannitol as an Inactive Ingredient in Approved Drug Products

Approved Drug Product	Mannitol Amount per Vial	Maximum Daily Intake (MDI) of Mannitol	Maximum Intake per Treatment Course
VIBATIV (telavancin hydrochloride injection, powder, lyophilized, for solution) 750 mg/vial	937.5 mg	875 mg/day[a]	18375 mg[b]
ERAXIS (anidulafungin injection, powder, lyophilized, for solution) 100 mg/vial	500 mg	1000 mg/day[c]	21500 mg[d]

[a] MDI is based on the maximum daily dose of telavancin of 700 mg [10 mg/kg x 70 kg (average adult body weight) = 700 mg]. MDI = MDD telavancin ÷ telavancin vial content x mannitol vial content (700 mg telavancin ÷ 750 mg telavancin/vial x 937.5 mg mannitol/vial = 875 mg mannitol).

[b] Maximum possible intake is based on the maximum daily intake of mannitol multiplied by the maximum possible duration of treatment episode (875 mg/day x 21 days = 18375 mg).

[c] MDI is based on the maximum daily dose of anidulafungin of 200 mg. MDI = MDD anidulafungin ÷ anidulafungin vial content x mannitol vial content (200 mg anidulafungin ÷ 100 mg anidulafungin/vial x 500 mg mannitol/vial = 1000 mg mannitol).

[d] Maximum possible intake is based on the maximum daily intake of mannitol for the expected duration of one day plus the maximum daily intake during continued therapy (500 mg) for the remaining days of the maximum possible duration of treatment episode (1000 mg/day x 1 day + 500 mg/day x 41 days = 21500 mg).

Table was obtained from page 10 of Quality Information Amendment in Response to IR Comments Received on 2020Nov24.pdf (SDN 9)

The most common adverse reactions with mannitol are hypersensitivity reactions, renal failure, CNS toxicity, hypo/hypervolemia, hypo/hyperkalemia, and infusion site reactions. However, these adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions. The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic/ hypersensitivity type reactions may occur when mannitol is used as an excipient. The intravenous injection of 10 g of mannitol daily over a period of 1 month produced no significant changes in non-protein nitrogen, CO_2-combining power of blood, red cell count, or renal function.

Given that the maximum daily intake and maximum total intake of mannitol are less compared to what has been administered as an approved drug product, or as an excipient in other approved drugs, the amount of mannitol in Dapzura RT is not expected to accumulate in the body or cause toxic effects.

B. Sorbitol for 6 weeks

Gammaplex (5%) is indicated for primary humoral immunodeficiency in adults and pediatric patients who are two years of age or older. The Gammaplex formulation contains 5 g of sorbitol per 100 ml. Gammaplex is administered intravenously at doses of 300 mg/kg to 800 mg/kg (6-16 mL/kg) every 3-4 weeks. The maximum infusion rate is 4 mg/kg/min. Therefore, for a 70 kg patient, 56 g of sorbitol is given with each dose. For a 6 week duration of treatment, patients would receive 112 g to 168 g of sorbitol compared with the 9.786 g of sorbitol given during a 6-week treatment course of Dapzura.

Neupogen (filgrastim) injection, solution was proposed by the Applicant as an example of an FDA approved drug containing sorbitol as an excipient. While many conditions treated using Neupogen are short term, it is also approved for daily use for severe chronic neutropenia (SCN) and studies show that patients may use the drug for years. The safety and effectiveness of Neupogen have been established in adult and pediatric patients with SCN. In the SCN postmarketing surveillance study, the reported median daily doses of Neupogen were: 6 mcg/kg (congenital neutropenia), 2.1 mcg/kg (cyclic neutropenia), and 1.2 mcg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of Neupogen greater than or equal to 100 mcg/kg/day. Considering this worse case exposure in a 70 kg adult patient, this would result in a total daily dose of 7000 mcg filgastrim. Although Neupogen for SCN is typically administered subcutaneously, Neupogen is also approved for intravenous administration. Equivalent doses are administered subcutanenously and intravenously. Use of the 300 mcg/ml product would result in an administration volume of approximately 23.3 ml. Each 1 ml 300 mcg single dose vial of Neupogen also contains 50 mg of sorbitol, therefore, a patient would be exposed to approximately 1165 mg of sorbiotol each day and a total of 48930 mg of sorbitol in 42 days.

Approved Drug Product	Sorbitol amount per ml	Maximum Daily Intake (MDI) of Sorbitol	Maximum Intake per Treatment Course
Gammaplex (Immune Globulin Intravenous (Human), 5% liquid 50 mg/ml	50 mg	56 g/day	112000 mg – 168000 mg
Neupogen (filgrastim injection, solution) 300 mcg/1.0 mL vial	50 mg	1165 mg/day	48930 mg

Sorbitol has been used in some parenteral nutrition (PN) products marketed outside the U.S. to act as an alternative to glucose as an energy source. Originally, this was thought to be advantageous because sorbitol is less insulin-

dependent, less ketogenic and better utilized in patients with glucose intolerance; it also enhances protein sparing.

The Applicant compiled a summary of published studies of parenteral nutrition products containing sorbitol at concentrations and durations of exposure equivalent to or higher than those in Dapzura RT (SDN12; submitted 1/27/2021). Most of studies were conducted in Europe. In the PN preparations, the content of sorbitol was significantly more than the content of sorbitol in a single 10 mL vial of Dapzura RT (see Table 5).

Table 5. Sorbitol Content in Dapzura RT versus Parenteral Nutrition (PN) Preparations

Name of Preparation	Function of Sorbitol	Volume of Preparation (mL)	Sorbitol Content in Preparation (g)	Sorbitol Concentration (g/L)	Minimum Volume of Preparation to exceed MDI of Daptomycin (mL)[c]
Baxter's Daptomycin Formulation	Inactive Ingredient	10 mL	0.238	23.8[b]	N/A
Parenteral Nutrition Preparations					
Sorbitol 30%[2]	Active Ingredient	1 L	(b) (4)		
Aminoplex 5[a, 2]	Active Ingredient	1 L			
Trophysan 10[a, 2]	Active Ingredient	1 L			
Lipiphysan[a, 3]	Active Ingredient	1 L			
Lipofundin[a, 3]	Active Ingredient	1 L			

[a] These PN preparations contain other active ingredients besides sorbitol that are not listed in this table.

[b] While the sorbitol concentration in Baxter's Daptomycin formulation is 23.8 g/L, the maximum volume to be delivered is much smaller than that associated with PN preparations and the resulting sorbitol exposure is much lower

[c] Calculated as Maximum Daily Intake of Baxter's Daptomycin formulation (0.233 g) divided by the Sorbitol Concentration in the preparation

Table was obtained from page 4 of quality-info-amend-response-ir-comment-2021jan06.pdf (SDN 12)

The amount of sorbitol that will be administered parenterally from Baxter's Daptomycin formulation in a single day would be approximately 0.233 g in 30 minutes (i.e., 0.00776 g/minute) if the patient is administered the drug via IV infusion or 0.233 g in 2 minutes (0.1165 g/minute) if the drug is administered as an injection. In contrast, if a patient on PN required 1200 calories from sorbitol (i.e. approximately 60% of energy requirements from carbohydrate sources) considering that 1 g of sorbitol would give 4 calories, then a patient would have been administered at least 300 g of sorbitol in a single day. Generally, the use of PN products is not limited for any number of days and if required may be administered for longer than 42 days.

Upon parenteral administration, sorbitol is metabolized to fructose by sorbitol dehydrogenase (polyol dehydrogenase) and thereafter its metabolism is the same as that of fructose. The main sites of sorbitol metabolism are the liver and to a lesser extent the kidney, and in healthy subjects the maximum turnover capacity for sorbitol is around 0.5 g/kg/h. However, multiple studies have observed that during intravenous administration of sorbitol at rate of 0.5 g/kg/h, subjects experienced nausea, epigastric pain, and vomiting and it was determined that the maximum safe infusion rate for sorbitol in adults is 0.25 g/kg/h (0.004167 g/kg/min). Newton et al. (1978) noted that the discrepancy between the maximum turnover capacity (0.5 g/kg/h) and the maximum safe infusion rate (0.25 g/kg/h) is because the maximum safe infusion rate takes into consideration not only the rate of removal of the infused nutrient, but also the rate of formation or loss of intermediates, the rate of formation of metabolic end products, rate of removal of major metabolic products, and effects of underlying disease.This maximum safe infusion rate of 0.25 g/kg/hour with a total of 1.5 g/kg/day (i.e., approximately 0.25 g/kg/hour for 6 hours) was also recommended by German health authorities when PN formulations containing sorbitol were still in use.

Considering the weight of an average patient (70 kg) being administered the maximum dose of daptomycin, the maximum infusion rate of sorbitol would be multiple times less than the maximum safe infusion rate identified above when Dapzura RT is administered according to the 2-minute infusion instructions in the labelling (0.1165 g/minute ÷ 70 kg = 0.00166 g/kg/minute), and the sorbitol infusion rate would be even less if daptomycin is infused via a 30-minute infusion. The maximum daily intake and the maximum possible intake of sorbitol over the treatment course (0.233 g x 42 days = 9.79 g) from Dapzura RT would also be significantly less than the total safe dosages per day observed with PN (Table 6).

Table 6. Sorbitol exposure from Dapzura RT compared to PN preparations

Name of Preparation	Sorbitol Maximum Daily Intake	Sorbitol Maximum Exposure over a 42-day (i.e., 6 weeks) Treatment Course	Sorbitol Infusion Rate
Daptomycin Baxter Formulation	0.233 g[a]	9.79 g	0.000109 g/kg/min[c] if given as a 30 min infusion OR 0.00166 g/kg/min[c] if given as a 2 min injection
Parenteral Nutrition Preparations Administered According to Recommendations[b]	105 g[c]	4,410 g	0.004167 g/kg/min

[a] Considering a maximum dose of 490 mg of daptomycin

[b] Maximum safe infusion rate of 0.25 g/kg/hour with a total of 1.5 g/kg/day

[c] Considering a 70 kg individual

Table was obtained from page 6 of quality-info-amend-response-ir-comment-2021jan06.pdf (SDN 12)

A comparison of total daily dose and dosage rate of sorbitol administered to volunteers for the PN studies versus Dapzura treatments shown in Table 7.

Table 7. Total dosages and rates of sorbitol in PN versus Dapzura RT

	Sorbitol Administered as an Active Ingredient in PN in Healthy Volunteers						Sorbitol Administered as an Inactive Ingredient in Baxter's Daptomycin Formulation	
Citation	Forster et al., 1974[7]	Pellaton et al., 1978[8]	Bickel et al., 1973[9]	Matzkieset al., 1973[9]	Lee et al., 1972[1]	Chatamra et al., 1975[11]	**Daptomycin Infusion over 30 minutes**	**Daptomycin Injection over 2 minutes**
Sorbitol Administered as stated in publication	1.5 g/kg in over 20 min	0.36 g/kg/h for 2 hours	0.25 g/kg/h for 6 hours	0.5 g/kg/h for 9 hours	150 g (30%) in 5 hours	Aminoplex 5[a] for at least 1 hour at a rate of 1 L/ 6 h	N/A	N/A
Sorbitol Dosage Considering a 70 kg Patient (g)	105 g	50.4 g	105 g	315 g	150 g	Approx. 20 g	0.233g[b]	0.233g[b]
Sorbitol Dosage Rate (g/min)[c]	5.25	0.42	0.29	0.58	0.5	0.33	0.00776[d]	0.1165[d]

[a] Aminoplex 5 contains 125 g of sorbitol per Liter

[b] The maximum daily intake based on the maximum daily dose of daptomycin

[c] Calculated as the Sorbitol dosage considering a 70 kg patient (in g) divided by the duration of infusion in minutes

[d] Calculated as the maximum possible daily intake divided by the duration of infusion/injection in minutes

The Applicant summarized the literature regarding adverse events associated with intravenously administered sorbitol, including the incidence of lactic acidosis and oxalate meningitis, and the doses and duration of intravenously administered sorbitol that resulted in these adverse events.

In the publications described, sorbitol in PN preparations was administered to over 70 patients. The overall evidence shows effects such as increase in blood lactate concentrations leading to acidosis, increase in serum uric acid, transaminases, and formation of oxalate crystals may be possible with the administration of sorbitol. Other adverse events included changes in plasma electrolyte concentration, epigastric pain, tachycardia, fainting, and nausea and vomiting. However, these effects are strongly dependent on the rate, duration and dose of infusion, and risk is increased especially if the maximum safe infusion rate of 0.25 g/kg/h is exceeded or when doses higher than 1.5 g/kg/day were administered. Given the maximum daily intake of sorbitol from Dapzura RT and duration over which this is administered via infusion or via injection, the maximum safe infusion rate is not exceeded, and it is therefore unlikely that these AEs will occur with Dapzura.

In studies including pediatric patients administered PN containing sorbitol, the infusion rates for sorbitol were higher than the maximum safe infusion rate in adults of 0.25 g/kg/h. In the study by Principi et al., (1973) there was only one patient whose acid-base balance was shifted towards acidic values with infusion rates ranging from 1 g/kg/h to 0.7 g/kg/h lasting at least 9 hours. In the study by Aynsley-Green et al., (1974), overall sorbitol dosages were less than those used by Principi et al., (1973) but administration rates were higher. The study showed that all patients had an increase in blood lactate concentrations, with the children given the higher infusion rates having a greater increase. The lactate pyruvate ratio also increased at the end of the infusion with the effect also being dose related. Despite these effects, the study concluded that infants can compensate satisfactorily for the rise in organic acid concentrations, and in fact, no changes in partial blood pressure of oxygen or carbon dioxide were observed.

The Applicant provided four case reports of lactic acidosis found in the literature. Patients exposed to sorbitol exceeding 0.25 g/kg/h or those with hepatic and renal impairment are more prone to lactic acidosis. The Applicant provided 16 cases of formation of oxalate crystals in the brain. In most of the cases, sorbitol was given in combination with other products such as fructose or xylitol. One case showed that a patient received only 105 g of sorbitol and no other sugar surrogates, and intensive oxalate deposition occurred. In another case, 18.5 g of sorbitol was administered in combination with 44 g of mannitol on a single day and distinct oxalate crystals were visible upon neuropathological examination of the brain. As previously noted, a 42-day treatment course of Dazpzura RT would expose the patient to 9.786 g of sorbitol, which is significantly less than the doses that cause oxalate crystals in these reports.

Given the maximum daily intake of sorbitol from Dapzura RT and duration over which it is administered via infusion or injection, the maximum safe infusion rate is not exceeded, and it is highly unlikely that lactic acidosis, oxalate

meningitis and other adverse events identified from the literature will occur with Dapzura.

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