Prepared omadacycline for injection: Nine-day stability and sterility in an elastomeric pump

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Abstract

Objective: To investigate compatibility, stability, and microbiologic risk of omadacycline 1 mg/mL when prepared in an elastomeric infusion pump and stored under refrigeration for 9 days based upon requests for information from healthcare providers.

Methods: Omadacycline was reconstituted to 1 mg/mL with sodium chloride 0.9% w/v or dextrose 5% w/v in SMARTeZ® elastomeric infusion pumps and refrigerated for up to 9 days. Samples were taken daily and tested for appearance, pH, osmolality, chemical composition, and particulate matter. For a microbial challenge study, the pumps were spiked with a challenge microorganism (Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, or Aspergillus brasiliensis) and samples were plated daily for 9 days to assess microbial survival.

Results: Appearance, pH, osmolality, percent label claim, and particulate matter results remained essentially unchanged for omadacycline solutions in either diluent over the 9-day study. No >0.5-log day-to-day increases in the challenge-microorganism populations were measured in diluted omadacycline pumps or positive controls. With omadacycline, no growth was seen for S. aureus or E. coli in either diluent, nor for P. aeruginosa in dextrose 5% w/v. Reduction of C. albicans and A. brasiliensis populations over time was similar between omadacycline solutions and positive controls.

Conclusion: After reconstitution, omadacycline for injection was stable and remained within specifications for use for up to 9 days when refrigerated.

Keywords

Antibacterial agents, tetracycline, drug stability, microbial colony count, elastomeric pump system

Introduction

Omadacycline, a novel aminomethylcycline derived from the tetracycline class of antibiotics, is approved by the US Food and Drug Administration as once-daily intravenous (IV) and oral therapy for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. For these indications, omadacycline IV requires a loading dose on Day 1 of 100 mg IV Q12 or 200 mg IV once then a maintenance dose of 100 mg IV daily. For patients not requiring IV therapy, omadacycline has a bioequivalent oral formulation that may also be used for both indications.1–3 Local preparation procedures are necessary for IV administration, and data on any changes that may occur subsequent to initial preparation are informative for the real-world needs of patients. In addition to potential time-dependent physical and chemical changes, microorganism contamination during preparation is a risk that might result in microbial growth during postdilution storage. Prior studies of omadacycline 1 mg/mL (100 mL) prepared in an infusion bag have demonstrated room temperature stability for 24 h or 7 days when refrigerated.4

Omadacycline for injection may be provided to patients within other devices such as an elastomeric infusion pump. This requires stability and sterility beyond 7 days to accommodate weekly deliveries to patients, and, therefore, additional

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assessments were needed. This study investigated the physical and chemical changes to omadacycline for injection and the growth potential of microorganisms following reconstitution to 1 mg/mL (typical concentration for patient use) in refrigerated elastomeric infusion pumps over 9 days.

Methods

The objective of this study was to provide an assessment of omadacycline IV stability and sterility when compounded within the SMARTeZ® elastomeric infusion pump as per the reconstitution and dilutions instructions for omadacycline and refrigerated for 9 days. This study was completed on 5–28 March 2019.

Reconstitution of omadacycline in product vials

Omadacycline for injection (Paratek Pharmaceuticals, Inc., Boston, MA) was supplied in rubber-sealed glass vials containing 100 mg omadacycline as a lyophilized powder (equivalent to 131.1 mg omadacycline tosylate). The manufacturing process has been validated and approved per New Drug Application (NDA) 209817 to consistently produce lyophilized product that is between 95 and 105 mg of active omadacycline per vial. Reconstitution was performed in accordance with the prescribing information on the same day as admixture preparation. At room temperature in either a laminar flow hood or a biosafety cabinet, 5 mL of Water for Injection (United States Pharmacopeia (USP)) was injected through the rubber seal, and liquid in the vial was gently swirled until all of the solid had visibly dissolved (≥2 min). With negligible powder volume, each reconstituted vial contained omadacycline at ~20 mg/mL (100 mg/5 mL total volume).

Choice of elastomeric pump and study duration

The SMARTeZ® elastomeric infusion pump (Epic Medical, Singapore) was chosen for this study because healthcare providers most often requested additional data about this device from the Medical Information Center for Paratek Pharmaceuticals, Inc. The study duration of 9 days was chosen to accommodate weekly deliveries to patients, allowing an extra 2 days for preparation and travel time. All preparations were allowed to warm to room temperature for 30 min before testing to reflect administration instructions in the prescribing information.

Preparation of admixtures

The admixtures were prepared in accordance with the prescribing information under artificial ambient lighting by Alcami Corporation (Durham, NC) personnel. The entire contents (5 mL) of the reconstituted omadacycline vial were transferred via the fill port into a SMARTeZ® pump, previously filled by syringe via the same fill port with 95 mL of diluent (either sodium chloride 0.9% w/v or dextrose 5% w/v) from an IV bag. Hence, the reconstituted omadacycline was diluted to a final concentration of 1 mg/mL, which is yellow/orange in color. In addition, selected analyses required negative-control admixtures (substitution of 5 mL Water for Injection for omadacyline) in both sodium chloride 0.9% w/v and dextrose 5% w/v.

All admixtures (including controls) were mixed by inverting them at least 10 times. After any further experimental treatment (see below), the pumps were primed by temporally removing the patient-end cap and opening the on/off clamp sufficiently to purge all air from the tube before the pumps were stored in unlit refrigerated conditions (2–8°C).

Although the prescribing information also allows for 2 mg/mL omadacycline dosing (200 mL or two vials per pump), in practice this is used almost exclusively for a one time loading dose, and the maintenance dose is 1 mg/mL. We, therefore, limited this study to the 1 mg/mL concentration.

Chemical analyses

For each of the two diluents, two pumps (duplicates) containing omadacycline and one negative-control pump were prepared for chemical testing (six pumps total). Two samples were analyzed for chemical composition and impurities and are representative of the entire lot per the approved NDA specification for release and stability for the available commercial product. Due to volume constraints, particulate matter testing additionally required three pumps containing omadacycline and one negative-control pump for each of the two diluents (eight pumps total).

Sampling schedule and procedure. Sodium chloride 0.9% w/v and dextrose 5% w/v admixtures were sampled in the same way each day, with a day defined as an elapsed period of 24 h since preparation, and within ±1 h of the 24-h time point. All pumps were allowed to warm to room temperature for 30 min before sampling. All samples were collected within a laminar flow hood or biosafety cabinet. Just before sampling, sampling sites were wiped with an isopropyl alcohol-prepared pad. Infusion pumps were inverted at least 10 times, and the first milliliter of sample released from opening the on/off clamp was discarded. Either 7 mL (chemical tests) or 30 mL (particulate matter test) was collected by flow into either plastic centrifuge tubes or sterile, lidded specimen containers, as appropriate. The infusion pump was then promptly returned to refrigerated storage.

Admixtures designated for chemical testing (appearance, pH, osmolality, and assay/related substances) were sampled within 1 h of preparation (Day 0). Each duplicate pump containing omadacycline for chemical testing was then sampled daily up to Day 9. After the values for pH, osmolality, and assay/related-substance testing were obtained, it was determined whether they met the prespecified acceptance criteria; if they did, the values from the duplicate pumps were...
averaged and the average value was reported. If either value was outside of the prespecified acceptance criteria, the values would be reported individually. Control admixtures were sampled again only on Day 9.

Admixtures designated for particulate matter testing provided three samples per admixture. Three infusion pumps were used to span the 9-day study period, with the first pump used for Days 0–2, and the second and third pumps used for Days 4–6 and 7–9, respectively (no sample was taken on Day 3). Control admixtures were sampled initially and on Day 9.

**Testing.** The visual appearance of each omadacycline-containing sample was recorded, with the acceptance criterion being continuance of the anticipated “clear solution from yellow to dark orange, essentially free from visible particulates.” The same undiluted samples were then pH tested using a glass electrode (Orion Versa Star 10; Thermo Scientific, Waltham, MA) and osmolality was analyzed (Model 3320; Advanced Instruments, Norwood, MA), with the acceptance criterion being no or negligible change over time.

Microbiological analyses

In total, 22 admixtures were prepared (11 for each diluent); five admixtures of omadacycline per diluent; six admixtures per diluent prepared with Water for Injection only (five positive controls and one negative control).
Preparation of microbiological controls. To test whether the omadacycline preparation would permit the growth of bacteria, microbial challenge experiments were conducted. Positive- and negative-control admixture preparations used 5 mL of Water for Injection held at a monitored room temperature for 1 h to simulate the drug dilution. Positive controls were inoculated (see below) with one of five challenge microorganisms recommended in Chapter 51 of USP6 and supplied by Microbiologies Inc. (St. Cloud, Minnesota, USA): *Staphylococcus aureus* (ATCC #6538), *Escherichia coli* (ATCC #8739), *Pseudomonas aeruginosa* (ATCC #9027), *Candida albicans* (ATCC #10231), or *Aspergillus brasiliensis* (ATCC #16404). The negative control was not inoculated and was sampled only twice (immediately after mixing and on Day 9).

Inoculation of preparations. Inocula for each of the five challenge microorganisms were prepared to deliver <100 colony-forming units (CFU) per plated aliquot of 1 mL of sample volume. Each test and positive-control admixture was inoculated with the appropriate microorganism inoculum by using a 1 mL syringe and mixed by gently inverting the pump for 10–15 seconds. Sterile scissors were used to snip the plastic patient-end tubing between the on/off clamp and the in-line filter for each pump. All inoculations and sample collections were performed within a biosafety cabinet.

Sampling schedule and procedure. Following inoculation, the first sample was removed (recorded as Day 0) and plated as described below. All pumps were stored in refrigerated conditions (2–8°C) for up to 9 days, only being removed for daily sampling. A day was defined as an elapsed period of 24 h since addition of the inoculum (negative controls excepted).

The on/off clamp on the patient-end tubing was opened to allow 2.5 mL to be collected by flow into a sterile test tube. The tubing clamp was then closed to stop further flow, and the end of the tubing was folded over and secured to keep the pathway sterile for testing on later days. The pump was then remixed before promptly being returned to refrigerated storage.

Plate-count procedure. Test samples were transferred into sterile Petri dishes immediately after sampling. Aliquots (1 mL) in duplicate Petri dishes were covered with either sterile tryptic soy agar (TSA with 0.5% lecithin and 4% polysorbate 20) or—for *C. albicans* and *A. brasiliensis*—sterile Sabouraud dextrose agar (SAB with 0.5% lecithin and 4% polysorbate 20). Agar was tempered according to standard practice (i.e. ≤45°C). Plates were allowed to solidify, inverted, and incubated for 3–5 days at 30–35°C, except for SAB plates containing *C. albicans*, incubated at 20–25°C for 3–5 days, or *A. brasiliensis*, incubated at 20–25°C for 3–7 days. A Quebec darkfield colony counter (Reichert, Inc., Buffalo, NY) was used to determine the number of CFU per plate.

Microbiological analysis. The acceptance criterion was that the initial inoculation level, as determined by the positive-control counts on Day 0, must be <100 CFU/mL. Results are presented as mean of duplicate sample CFU/mL and log difference of the end-of-study sample from Day 0. The log difference of the current daily sample from the previous daily sample was also investigated.

Results

All duplicate samples met prespecified acceptance criteria for pH, osmolality, and assay/related-substance testing; the values reported are an average of the duplicate pumps.

Visual appearance

For both sodium chloride 0.9% w/v and dextrose 5% w/v, omadacycline-containing samples were recorded as “clear yellow solution, essentially free from visible particulates” on Day 0 and did not change throughout the 9-day study, and so conformed to the acceptance criteria. Furthermore, no time-dependent visual differences were observed between omadacycline-containing samples and the control samples.

pH

The pH of all omadacycline-containing samples in either diluent met the acceptance criteria of negligible pH change over 9 days compared with Day 0. Sodium chloride 0.9% w/v samples were pH 4.2 on Day 0 and all other days except Days 5 and 6 (pH 4.3). Dextrose 5% w/v samples were pH 3.9 on Day 0 and all other days except Days 5–7 (pH 4.0). These differences in pH of 0.1 are within the tolerance of the instrument.

Osmolality

The osmolality of omadacycline-containing samples did not change significantly over time in either diluent during the study, indicating that storage does not affect the number of solute particles per kilogram of solution over 9 days. Osmolality was slightly higher for omadacycline solutions in sodium chloride 0.9% w/v (278–279 mOsmol/kg) than in dextrose 5% w/v (259–261 mOsmol/kg).

Assay and related substances

All %LC results for omadacycline reported in this study are within the range for the typical specification limits for omadacycline drug product lyophilized vials (95–105%) (Table 2). There were no noticeable trends in the assay results over time, and the variability seen is within the tolerances of the validated analytical method. The %LC acceptance criterion (≤5% change from Day 0) was met for all
Table 2. Quantification of omadacycline in refrigerated pumps by HPLC assay for each study day.

| Omadacycline | Diluent         | Day 0  | Day 1  | Day 2  | Day 3  | Day 4  | Day 5  | Day 6  | Day 7  | Day 8  | Day 9  | Acceptance |
|--------------|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------------|
| %LC          | NaCl 0.9% w/v    | 98.1  | 98.3  | 98.2  | 98.3  | 98.7  | 98.7  | 98.5  | 98.7  | 98.7  | 98.3  | 95–105 mg |
|              | Dextrose 5% w/v  | 96.6  | 96.0  | 95.9  | 96.0  | 95.9  | 96.3  | 96.1  | 96.2  | 96.3  | 95.9  |            |
| % of Day 0 (%LC) | NaCl 0.9% w/v | 100   | 100.2 | 100.1 | 100.2 | 100.6 | 100.4 | 100.6 | 100.6 | 100.2 | 100.2 |            |
|              | Dextrose 5% w/v  | 100   | 99.4  | 99.3  | 99.4  | 99.3  | 99.7  | 99.5  | 99.6  | 99.7  | 99.3  |            |

Table 3. Quantification of related substances and unknown impurities by HPLC assay in refrigerated pumps for each study day.

| Component | Diluent         | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Acceptance |
|-----------|-----------------|------|------|------|------|------|------|------|------|------|------|------------|
| 4-beta epimer omadacycline | NaCl 0.9% w/v | 2.90 | 3.05 | 3.08 | 3.08 | 3.11 | 3.21 | 3.22 | 3.20 | 3.21 | 3.29 | <6.8       |
| 7-monomethyl-omadacycline | Dextrose 5% w/v | 2.85 | 3.07 | 3.09 | 3.13 | 3.14 | 3.38 | 3.41 | 3.38 | 3.41 | 3.54 |            |
| Hydroxy-omadacycline | NaCl 0.9% w/v | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | <0.5       |
| Dehydro-omadacycline | NaCl 0.9% w/v | <0.09 | <0.09 | <0.09 | <0.09 | <0.09 | <0.09 | <0.09 | <0.09 | <0.09 | 0.12 | 0.12       |
| 4-keto-omadacycline | Dextrose 5% w/v | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05       |
| RRT 0.93 | NaCl 0.9% w/v | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 | <0.05       |
| RRT 1.29 | Dextrose 5% w/v | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05       |
| Total related substances | NaCl 0.9% w/v | 3.11 | 3.27 | 3.31 | 3.30 | 3.34 | 3.44 | 3.50 | 3.48 | 3.48 | 3.70 | 3.83       |

HPLC: high-performance liquid chromatography; NaCl: sodium chloride; RRT: relative retention times in HPLC.

*Lower limit of detection.

The %LC of 2 unknown impurities at relative retention times 0.93 and 1.29 were observed to increase from <0.05% (the limit of detection) up to 0.06% (Table 3); though the growth was minuscule, these impurities were not detected in the control pump (containing no drug product), suggesting that these small unknown degradation products might be related to the active compound.

All known and unknown impurities detected during the aging of omadacycline in the sodium chloride 0.9% w/v and dextrose 5% w/v admixtures were well below the IV vial release specification.

Particulate matter

The particulate matter results showed no meaningful differences over 9 days in both sodium chloride 0.9% w/v and dextrose 5% w/v. When not recorded as zero, particle counts remained minimal (maximum of 2 particles/mL ≥10 µm in diameter and 1 particle/mL ≥25 µm in diameter). The maximum particle count remained below the release specification (5 particles/mL at any time).
recording for the control pumps was <1 particle/mL. All particulate matter results remained within the manufacturer’s specification limits for particulate matter within the vial.

**Microbiology**

The study met the acceptance criterion for initial (Day 0) inoculation levels being <100 CFU/mL for each microorganism in the positive controls of sodium chloride 0.9% w/v (Table 4) and dextrose 5% w/v (Table 5). Negative controls for both diluents showed no growth (0 CFUs) initially and at the end of the study.

No increase in challenge-microorganism populations was evident when comparing the initial time point (Day 0) to the final time point (Day 9) in omadacycline samples diluted with either sodium chloride 0.9% w/v (Table 4) or dextrose 5% w/v (Table 5). No day-to-day increases in the challenge-microorganism populations greater than 0.5 log10 units (3.16 times) were measured in either diluted omadacycline samples or positive controls.

No microbial growth, as measured by CFUs, was observed with diluted omadacycline samples for *S. aureus*, *P. aeruginosa*, or *E. coli* in sodium chloride 0.9% w/v diluent or dextrose 5% w/v diluent (Tables 4 and 5). Reduction of *C. albicans* and *A. brasiliensis* populations over time was similar between diluted omadacycline and positive controls.

**Discussion**

The stability and sterility of compounded products are important for patient safety and should be informed by best practices and evidence from the assessment of similar products with similar endpoints. This study assessed a SMARTeZ® device based upon requests from healthcare providers for additional stability and sterility data with this device. Patients in which the SMARTeZ® device is not available may utilize omadacycline as prepared in the prescribing information with a standard infusion bag administered using gravity or an additional pump.

The results of this longitudinal study of omadacycline for injection met all acceptance criteria, demonstrating compatibility, stability, and low risk of advantageous bacterial growth for reconstituted omadacycline for injection (100 mg/vial) when it is diluted to 1 mg/mL in either sodium chloride 0.9% w/v or dextrose 5% w/v and stored in refrigerated SMARTeZ® elastomeric infusion pumps for 9 days. Variability that was seen for each diluent, 0.4 pH units and 1 or 2 mOsmols/kg, likely reflects variability in the measurement device.

Limitations of this analysis include that the admixtures were laboratory-prepared solutions to mimic real-world practice and, therefore, it would be prudent that this information be applied only when real-world compounding practices reflect the methods of this study. This analysis adds to the administration options for IV omadacycline, SMARTeZ® device, and infusion bag, but should not be applied to other devices. Finally, although the deliberate microbial contamination had short-lived microbial survival, any microbial contamination can have serious consequences for patients. This information is informative but not a substitute for compliance with current sterile compounding guidance.

**Conclusion**

This study demonstrates that the appearance, pH, osmolality, %LC, and particulate matter results remained essentially unchanged, and inoculated microorganisms showed no growth in solutions of omadacycline in either sodium chloride 0.9% w/v or dextrose 5% w/v during the 9-day stability period with refrigerated SMARTeZ® elastomeric infusion pumps. The study objectives were met and provided additional stability and sterility data for omadacycline in the SMARTeZ® elastomeric pump.
Table 5. Growth of challenge microorganisms in refrigerated pumps containing dextrose 5% w/v with or without omadacycline.

| Microorganism | Treatment   | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Log change (Day 0–End) |
|---------------|-------------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------------------------|
| S. aureus     | Omadacycline | 0    | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | NLD                     |
|               | Control     | 16   | 7     | 3     | 0     | 1     | 0     | 0     | 0     | 0     | 0     | NI                       |
| P. aeruginosa | Omadacycline | 0    | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | NLD                     |
|               | Control     | 11   | 1     | 0     | 1     | 0     | 0     | 0     | 0     | 0     | 0     | NI                       |
| E. coli       | Omadacycline | 0    | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | NLD                     |
|               | Control     | 34   | 15    | 2     | 2     | 2     | 0     | 0     | 0     | 0     | 0     | NI                       |
| C. albicans   | Omadacycline | 21   | 7     | 4     | 1     | 1     | 1     | 0     | 0     | 0     | 0     | NI                       |
|               | Control     | 21   | 10    | 4     | 1     | 0     | 0     | 0     | 0     | 0     | 0     | NI                       |
| A. brasiliensis| Omadacycline | 33   | 5     | 3     | 2     | 0     | 1     | 0     | 1     | 0     | 0     | NI                       |
|               | Control     | 30   | 13    | 3     | 4     | 0     | 2     | 1     | 0     | 0     | 0     | NI                       |

CFU: colony-forming units; NI: no increase; NLD: no log difference.

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Data availability statement
Paratek Pharmaceuticals, Inc., has a commitment to ensure that access to study data is available to regulators, researchers, and trial participants, when permitted, feasible and appropriate. Requests for de-identified patient-level data may be submitted to medinfo@paratekpharma.com for review.

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Supplemental material
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