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RESEARCH

# A multi-centre, phase IV study to evaluate the steady-state plasma concentration and serum bactericidal activity of a generic teicoplanin preparation

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**Introduction:** Teicoplanin is an effective treatment option against methicillin-resistant, Gram-positive bacteria, like *Staphylococcus aureus*. It is a glycopeptide antibiotic, produced through microbial fermentation, a process resulting in variations in the *N*-acyl side chain. Concerns that these variations may affect the pharmacokinetic profile and the clinical efficacy of generic teicoplanin preparations have been raised.
**Method:** To address this issue, a multi-centre observational study was conducted to evaluate steady-state peak and trough serum concentrations, and the serum bactericidal activity (SBA) and safety of a generic teicoplanin preparation in critically ill patients. Additionally, the composition of the generic teicoplanin was compared to that of the innovator drug to assess differences in the composition.
**Results:** Following pre-determined loading and maintenance dose schedules, the mean peak and trough teicoplanin serum concentrations were 20.98 mg/l and 10.38 mg/l, respectively. A statistically significant association was observed between teicoplanin pharmacotherapy and increased ex vivo SBA. It was found using independent analysis that the composition of the generic teicoplanin preparation was similar to that of the innovator drug, and that both formulations met the *European Pharmacopoeia* specifications.
**Conclusion:** The loading and maintenance schedules employed in this study were effective in establishing therapeutic serum teicoplanin concentrations in critically ill patients. Evidence of bactericidal activity measured in patients' ex vivo serum samples, following treatment with the generic preparation, supports this finding.

**Keywords:** complex antibiotics, generic, peak and trough concentrations, pharmacokinetics, serum bactericidal activity, teicoplanin

## Introduction

Gram-positive bacteria cause a diverse range of healthcare-associated and community-acquired infections. Healthcare-associated infections have emerged as a particular source of concern as these infections are on the increase globally, especially in sub-Saharan Africa.[1] *Staphylococcus aureus* and enterococci are frequent sources of nosocomial infections, such as bacteraemia, pneumonia and skin and soft tissue infections. Of these, methicillin-resistant *S. aureus* (MRSA) is particularly problematic from a treatment perspective, owing to its multidrug-resistant nature.[2] Teicoplanin is an effective treatment option against antibiotic-resistant Gram-positive bacteria, like MRSA, and is reserved for pharmacotherapeutical interventions in cases of drug-resistant septicaemia, endocarditis, and infections of the skin and soft tissue, bone and joints, and the lower respiratory tract. A number of advantages are associated with the use of teicoplanin over other currently available glycopeptides. For one, it is appropriate as treatment for patients with fever and neutropenia, and in comparison with vancomycin, has a lower risk of nephrotoxicity, when combined with an aminoglycoside. Teicoplanin also has a lower incidence of anaphylactoid reactions when compared with vancomycin.[3]

Teicoplanin is a glycopeptide antibiotic, a class which includes vancomycin, telavancin, bleomycin and ramoplanin. The pharmacologically active ingredient, teicoplanin, refers to a group of structurally similar chemical entities, termed teicoplanin $A_{2-1}$ to $A_{2-5}$, which are microbial secondary metabolites produced by a number of non-ribosomal peptide synthetases to form a cyclic heptapeptide structure. The $A_{2-1}$ to $A_{2-5}$ structural forms account for 89–95% of active teicoplanin.[4] The different chemical entities in the teicoplanin $A_2$ group have identical chemical core structures, and differ only in a variable glucosamine *N*-acyl fatty acid side chain ranging in length from 9–12 carbons, with or without branching. The identical teicoplanin core consists of a seven amino acid, tetracyclic peptide backbone, with three sugar residues.

Teicoplanin has very low bioavailability when taken orally, but the intravenous and intramuscular routes of administration are associated with high bioavailability and are well tolerated. Only 2–3% of an intravenously administered dose of teicoplanin is metabolised, while approximately 90% is plasma protein bound.[5] Teicoplanin is extensively bound to albumin, with the free fraction estimated to be between 6 and 12%, which positively correlates

with the total serum teicoplanin concentration. A decrease in albumin levels and/or polypharmacy, leading to drug-drug interactions from shared protein binding sites is likely to reflect altered teicoplanin serum concentrations in intensive care unit patients.[6,7] The pharmacokinetics of teicoplanin are characterised by a long elimination half-life of 30–180 hours, implying that there is a prolonged period before steady-state concentration is achieved.[8] Therefore, an initial multiple-dose loading schedule was recommended to enable the rapid ach ievement of therapeutic serum concentrations. Therapeutically effective plasma concentrations of teicoplanin are achieved with minimal delay in most patients when appropriately high loading doses are administered, resulting in improved outcomes for patients with severe multidrug-resistant Gram-positive infections.[5,8] The optimal pharmacodynamical parameter of the area under the curve (AUC) (24 hours)/minimum inhibitory concentration (MIC), adequate teicoplanin serum and site of infection concentrations, as well as the MIC for the pathogen, are important determinants of therapeutic outcome.[9–11] Being non-ribosomal peptides, the glycopeptide antibiotics are generally synthesised by highly specific enzymes which are naturally expressed in some Actinobacteria. These peptides are large complex molecules which have an either cyclic or branched structure, and because of their complexity, large-scale synthetic production is not feasible. For this reason, these molecules are usually produced through microbial fermentation. Pharmaceutical-grade teicoplanin is produced by fermentation, using *Actinoplanes teichomyceticus*.[4] This method of production is inherently variable since the composition of a teicoplanin preparation produced by fermentation depends on a number of factors, including the biological, physical and chemical components of the process. As a result, the final teicoplanin composition created by different manufacturers may vary slightly.

Owing to the complex nature of these pharmaceutical preparations, strict criteria were implemented to control the composition of teicoplanin preparations. However, concerns have been raised recently about the clinical efficacy of teicoplanin preparations, other than the innovator drug. It is believed that variations in composition may alter the overall pharmacokinetic profile of a teicoplanin preparation to such an extent that therapeutic equivalence to the innovator drug is not possible.[12]

To address this issue, a post-marketing trial was conducted to assess the steady-state peak and trough serum concentrations in critically-ill patients treated with a generic teicoplanin preparation. Secondary objectives included the safety and bactericidal activity of the serum of patients who were treated with the generic teicoplanin preparation. Finally, the composition of the generic teicoplanin preparation was compared to that of the innovator drug by an independent, certified, testing facility using standardised methodology.

## Method

### *Ethical considerations*

Prior to commencement of the study, all ethical, scientific and medical aspects of the study were considered by a local independent research ethics committee, Pharma-Ethics. Approval of the protocol, an informed consent form and any other relevant study documentation were granted before commencing with any study procedures (Ref No 13035327). The study was registered with the South African National Human Research Ethics Council (Ref No 3726). Study procedures were carried out and essential documentation captured according to the approved protocol, the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human use: Guideline for Good Clinical Practice (GCP), the South African GCP guidelines and the World Medical Association Declaration of Helsinki. Owing to the nature of the trial, a standard operating procedure (ASP003-SOP001), specific to this trial, was implemented to address issues relating to consent if the subject was, among other things, incompetent, i.e. incoherent or unable to speak. Written informed consent was obtained from a legal representative, guardian or primary caregiver, such as a close relative, in these cases. An impartial witness was required to be present at the time that the consent was given.

### *Study overview*

This was a prospective, open-label, multi-centre, post-marketing, phase IV clinical study to evaluate the steady-state concentration and antimicrobial activity of a generic teicoplanin preparation in critically ill patients. Data were collected from eligible patients who were treated with Aspen Teicoplanin® 400 mg by their tending physicians in this observational study. The decision to use Aspen Teicoplanin® was at the discretion of the attending clinician.

A total of 37 patients from four hospitals and intensive care units in the Gauteng province of South Africa with severe, suspected Gram-positive infection, who required glycopeptide antibiotic treatment, were enrolled in this study. A loading schedule consisting of multiple doses was used to reduce the time until steady-state concentration was achieved. In brief, patients received an initial dose of 800 mg teicoplanin, either intravenously or intramuscularly, followed by three further doses of 400 mg, administered every 12 hours. A daily maintenance dose of 400 mg of teicoplanin was administered, either intravenously or intramuscularly, for at least three days, following the previously referred to loading schedule, except in two subjects, where the daily doses were adjusted to 200 mg, based on impaired renal function. The total duration of subject participation was approximately three weeks, including a two-day screening period, a five-day treatment period and a 14-day follow-up period.

Blood samples were drawn before the initiation of the teicoplanin treatment to determine the baseline teicoplanin values for both the serum concentration and serum bactericidal activity (SBA). Data on serum albumin, serum creatinine and estimated glomerular filtration rate (eGFR) were collected before treatment was initiated, as per standard hospital chemistry tests. Blood samples for culturing were drawn before treatment, as per standard hospital care. Serum teicoplanin was assumed to reach steady-state concentration after approximately five days of treatment, following the described dosing schedule. To determine the steady-state teicoplanin plasma concentrations, blood was drawn 2–4 hours after study drug administration of dosing for peak concentration, and 18–24 hours after study drug administration for trough concentration, on the fifth day. Serum albumin, serum creatinine and eGFR were measured on the same day. Duplicate blood samples were drawn at the same time points to determine SBA.

### *Inclusion and exclusion criteria*

Inclusion criteria were male and female patients aged 18 years or older, with suspected Gram-positive infections requiring treatment with a glycopeptide antibiotic. Volunteers were not eligible for participation if they were allergic to glycopeptide antibiotics, were pregnant or lactating, had participated in other clinical trials using teicoplanin, or if they were likely to die from

any cause in the 48 hours following enrolment. Since these were mostly critically ill patients, the last exclusion criterion was necessary in order to achieve the primary end-point of the study, i.e. the determination of steady-state plasma trough serum concentrations, estimated to occur five days after the dosing had started.

### *Serum teicoplanin concentrations*

Serum teicoplanin was determined using a liquid chromatography (LC)-tandem mass spectrometry (MS)/MS method, validated according to the ICH Q2(R1) guideline. An Agilent® 1100 Series HPLC system, coupled to an AB Sciex® 4000 QTRAP triple quadrupole mass spectrometer, was employed, using multiple-reaction monitoring in positive mode. Mass transitions determined to be suitable for the quantitation of teicoplanin (940.6 m/z → 316.5 m/z, and 940.6 m/z → 298.3 m/z) were consistent with the literature.[13] Erythromycin was used as an internal standard (734.5 m/z → 158.5 m/z, and 734.5 m/z → 576.9 m/z). Analytes were separated on an Alltech™ Alltima™ Reversed-Phase HPLC Column, 20 mm × 2.1 mm, with 3 µm particles. Mobile phases consisted of A: 0.1% formic acid in $_dH_2O$, and B: acetonitrile. Starting conditions were 10% organic phase and 90% aqueous. Following a 10 µl injection, staring conditions were held for 0.5 minutes, after which the organic phase increased to 30%; between 0.5 minutes and 5.0 minutes. The organic phase was then increased to 98%, between 5.0 minutes and 7.0 minutes, and was maintained at 98% for another two. Thereafter, starting conditions (10%) were re-established between 9.0 minutes and 10.0 minutes, and held for re-equilibration between 10.0 minutes and 12.0 minutes. The flow rate was maintained at 450 µl/minute at all times.

Teicoplanin was extracted using a protein precipitation method. Briefly, a total of 150 µl of well-mixed, thawed serum was transferred to a microcentrifuge tube, to which 450 µl of methanol (containing 0.2 µg/ml internal standard) was added. The mixture was then vortex mixed for 10 seconds, after which it was incubated in an ultrasonic bath at room temperature for 40 minutes. Following extraction, the mixture was centrifuged for 10 minutes at 16 000 × *g,* and 200 µl of the supernatant was transferred to an autosampler vial for LC-MS/MS analysis. Concentrations were measured by comparison to calibration curves established using teicoplanin-spiked plasma and the same methodology.

### *Serum bactericidal activity*

Three serum samples, representing a baseline, peak level and trough level, were used to inoculate a 96-well microtitre microplate. A total of 200 µl of serum from each sampling time point was added to the wells, in duplicate, to allow for the generation of six sampling time points from which to determine SBA. A control strain, *S. aureus* ATCC® 29213 was used to inoculate the samples. SBA was determined, as described previously, with the exception of a higher inoculum [$10^7$ colony forming units (CFUs)/ml] that was used to counter the effects of the serum.[14,15] Briefly, all serum samples were tested in duplicate with sampling and determination of the colony count at time points 0, 1, 2, 4, 6 and 18-24 hours. Linear regression analysis was used to assess the serum bactericidal rate (SBR), defined as the slope of the regression line. A negative slope to the line was defined as bactericidal activity, and the absolute value of the slope was representative of the rate of killing. The SBR unit of measurement was the change in $\log_{10}$ CFU/ml per hour of exposure. The baseline serum sample was utilised as a control to account for the intrinsic bactericidal activity of the collected serum and the effects of the concomitant medication. An additional control strain (*Escherichia coli* ATCC® 25922) was used as a positive growth control.

### *Composition of the generic teicoplanin preparation*

Three samples from three separate batches (batch numbers G-402, G-403 and G-404), of the generic teicoplanin preparation and the originator drug (batch numbers A3605, A3670 and A2531) were compared at the South African Bureau of Standards (SABS). The composition of the samples was analysed using high-performance liquid chromatography, according to methodology set out in the *European Pharmacopoeia*.[16]

### *Statistical analysis*

The primary end-point of the study was to determine whether steady-state trough serum concentrations were non-inferior to the therapeutic threshold of 10.0 mg/l.[5,17,18] The non-inferiority margin used was 1.4 mg/l, a quarter of the reported standard deviation (SD) (5.6 mg/l) of teicoplanin trough concentrations.[19] Analysis was performed using a one-sided, Student's one-sample *t*-test at the 0.05 level of significance. Normality of the data was established. Secondary end-points included SBA and safety. A Chi-squared test was used to test the association between teicoplanin treatment and SBA. Safety was assessed in terms of the incidence and severity of adverse events, and any changes in a patient's medical condition, physical examination findings and vital signs.

## Results

### *Patient demographics and safety outcomes*

Of the 37 patients initially recruited for the study, two patients withdrew their consent. One patient was discharged prior to the fifth day of treatment, and data from this patient were not included in analysis of the peak and trough teicoplanin levels. Two patients were underdosed because they had acute and chronic kidney failure, respectively, and since this was a serious protocol deviation, they were excluded from evaluation of the primary end-point. There were detectable serum teicoplanin levels at baseline in another patient, and therefore he or she was also excluded from the analysis set used to evaluate the primary end-point. The safety population ($n$ = 34) and the per protocol population ($n$ = 31) were the final-analysis populations. There were 12 men and 21 women with a mean age of 60.2 years in the safety population. The ages ranged from 26–89 years. There were three female patients of child-bearing potential, all of whom presented with a negative pregnancy test. The majority of patients, 31 (91.2%) were Caucasian. Two (5.9%) were coloured patients and 1 (2.9%) a black patient.

There were two deaths in the study population, both of which occurred after the patients had completed the study. One patient died as a result of an acute *Pseudomonas* infection, and the other as a result of subdural bleeding. Apart from these two serious adverse events, all of the patients recovered and all of the infections were treated successfully. In terms of safety, none of the survivors experienced worsening of any of the physical examination findings, their vital signs or medical condition. None of the recorded adverse events were deemed to relate to the study medication, and none of the patients were withdrawn from the study as a result of an adverse event. The most common adverse events experienced were nausea (17.9%), followed by diarrhoea (10.3%) and vomiting (7.7%). The mean (±SD) serum creatinine levels of subjects at screening and on the fifth day of treatment was 81.43 µmol/l (±53.70 µmol/l) and 65.59 µmol/l (± 38.68 µmol/l), respectively. The mean (±SD) glomerular filtration rate of subjects at screening and on the fifth day of

treatment was 30.25 ml/minute (±6.04 ml/minute) and 75.74 ml/minute (±18.68 ml/minute), respectively.

### *Serum teicoplanin concentrations*

The mean (± SD) peak serum concentration of teicoplanin at 2–4 hours after dosing on the fifth day of treatment was 20.98 mg/l (± 9.54 mg/l) [90% confidence interval (CI): 18.07–23.89]. The mean trough serum teicoplanin concentration was 10.38 mg/l (± 4.47 mg/l) (90% CI: 9.02–11.74) at 18–24 hours after dosing. Based on the non-inferiority margin of 1.4 mg/l, the mean teicoplanin trough levels (18–24 hours post dose) proved to be non-inferior to the therapeutic threshold of 10.0 mg/l ($p < 0.05$). The observed mean teicoplanin peak concentrations (2–4 hours post dose) were significantly higher ($p < 0.0001$) than the therapeutic threshold of 10.0 mg/l.

### *Serum bactericidal activity*

SBA was determined for 32 of the 37 enrolled patients. Patients whose serum was excluded from the SBA analysis were the two patients who withdrew their consent, as well as three patients whose samples were lost to contamination. Five (15.6%) of the peak samples and 5 (15.6%) of the trough samples demonstrated an increase in the number of CFUs, indicating insufficient bactericidal activity (SBA negative). Similarly, 27 (84.4%) of the peak samples and 27 (84.4%) of the trough samples showed a decrease in the number of CFUs, demonstrating bactericidal activity (SBA positive). There was no difference in the number of SBA-positive and SBA-negative samples between the peak and trough time points. The mean (± SD) SBR for the peak and trough serum samples was 0.076 $\Delta\log_{10}$ CFU/ml/hour (± 0.116 $\Delta\log_{10}$ CFU/ml/hour) and −0.083 $\Delta\log_{10}$ CFU/ml/hour (± 0.106 $\Delta\log_{10}$ CFU/ml/hour), respectively. Compared to baseline serum samples, the number of peak and trough serum samples demonstrating bactericidal activity differed significantly ($p < 0.05$) (Table 1).

### *Composition of the generic teicoplanin preparation*

On average, the generic teicoplanin preparation contained more teicoplanin $A_{2-2}$ and $A_{2-3}$ and less $A_{2-4}$ and $A_{2-5}$ than the innovator teicoplanin preparation (Table 2). The compositions of both the innovator and generic teicoplanin preparations met the requirements set out in the *European Pharmacopoeia* (Table 2).[16]

**Table 1:** Comparison of the number of baseline and peak or trough serum samples per group which demonstrated bactericidal activity

| | SBA (+) | SBA (–) | *p*-value* |
|---|---|---|---|
| Number of baseline serum samples | 19 | 13 | < 0.05 |
| Number of peak or trough serum samples | 27 | 5 | |

SBA (–): serum bactericidal activity (negative), SBA (+): serum bactericidal activity (positive).
*Estimated using a chi-square test.

## Discussion

The primary objective of this study was to assess teicoplanin steady-state peak and trough serum concentrations in patients after five days of treatment with Aspen Teicoplanin®, which included an initial loading dose schedule. Evaluation of the data confirmed that both the peak and trough levels of Aspen Teicoplanin® at steady-state concentration reached the minimum effective concentration. The observed mean trough level of 10.38 mg/l (± 4.47 mg/l) proved to be non-inferior to the therapeutic threshold for teicoplanin pharmacotherapy, i.e. 10 mg/l.[5,17,18] The observed peak level of 20.98 mg/l (± 9.54 mg/l) was approximately double that observed for the trough levels. The dosing schedule used in this study was effective in establishing the therapeutic steady-state serum concentrations of teicoplanin, and may serve as a useful guideline for rational teicoplanin pharmacotherapy in critically ill patients with suspected Gram-positive infections.

Side-effects previously reported with teicoplanin use include nephrotoxicity, hepatotoxicity and allergy, usually presenting as a skin rash.[20,21] One case of erythoema was reported, and there were elevated serum creatinine levels in four subjects, all of whom had already presented with elevated serum creatinine at screening. Overall, renal function improved in the sample between baseline and the fifth day of treatment. None of the reported adverse effects were deemed to be related to the product under investigation.

Bactericidal activity was assessed separately to support the pharmacokinetic findings of this study. A considerable number of samples demonstrated intrinsic SBA at baseline. This can be attributed to the fact that serum is bactericidal itself, and the majority of patients received one or more antibiotics as concomitant medication. Teicoplanin is not always a first-line antibiotic, and is often added or used as a substitute to an existing regimen. This was an acknowledged limitation of the SBA assessment, although a number of steps were taken to mitigate against this. The effect of concomitant medication was taken into account by determining the baseline SBA and considering the baseline SBA in the statistical analysis (Table 1). More than half the patients were on a concomitant antibiotic at baseline. Additionally, seven patients were not on another antibiotic at the time of serum sampling on the fifth day. Lastly, experimental conditions included the use of a positive growth control to monitor for extraneous antimicrobial activity, and the use of a higher inoculum to counter the activity of other agents, and ß-lactams, in particular. This leads us to believe that it is likely

**Table 2:** The relative composition of originator and generic teicoplanin preparations and composition requirements, as set forth in the *European Pharmacopoeia*

| Constituent | Targocid® | | ASPEN Teicoplanin® | | European Pharmacopoeia requirements[16] |
|---|---|---|---|---|---|
| | Median (%) | Range (%) | Median (%) | Range (%) | (%) |
| $A_{3-1}$ | 10.3 | 10.0–11.2 | 9.4 | 9.3–10.7 | ≤ 15 |
| $A_{2-1}$ | 11.7 | 5.2–12.5 | 13.7 | 3.5–13.8 | ≤ 20 |
| $A_{2-2}$ | 47.0 | 45.8–52.2 | 53.0 | 52.7–54.2 | 35–55 |
| $A_{2-3}$ | 5.6 | 5.2–5.9 | 10.4 | 6.4–10.5 | ≤ 20 |
| $A_{2-4}$ | 11.7 | 11.1–12.9 | 6.9 | 6.7–13.0 | ≤ 20 |
| $A_{2-5}$ | 12.7 | 12.1–13.9 | 6.0 | 5.7–12.2 | ≤ 20 |
| $A_{2\,total}$ | 88.5 | 87.1–89.7 | 89.6 | 89.3–89.7 | ≥ 80 |

that the resultant significant difference in baseline versus peak and trough SBA can be attributed to the activity of the teicoplanin. It should be noted that the recovery of patients in this study couldn't be attributed to teicoplanin pharmacotherapy alone since many of the participants received concomitant antibiotics.

Our SBA findings corroborated conclusions drawn from the pharmacokinetic observations. Both the peak and trough serum samples yielded negative SBRs, indicative of bactericidal activity. There was a statistically significant association between the number of SBA-positive trough serum samples and teicoplanin pharmacotherapy ($p < 0.05$) (Table 1), indicating that SBA increased following teicoplanin pharmacotherapy for five days. It is reasonable to attribute the increase, from baseline, in SBA, to teicoplanin pharmacotherapy. It was also noted that there was no difference between the SBA of the peak and trough serum samples. With the exception of one sample, in all cases where SBA was evaluated, the trough serum sample was found to be SBA positive if the peak sample was found to be SBA positive. This finding suggests that trough teicoplanin levels were above the therapeutic threshold for a Gram-positive test strain used (*S. aureus* ATCC® 29213), since an increase in the serum teicoplanin level was not associated with a greater number of SBA-positive samples.

Although it is unlikely that small variations in the composition of teicoplanin preparations will significantly affect the biological activity and/or safety thereof, regulatory authorities require that the composition of complex generic preparations is similar to that of the approved innovator drug.[4] To delineate the aforementioned, the *European Pharmacopoeia* describes limits and specifications pertaining to the relative abundance of the individual members of the teicoplanin group of compounds (Table 2).[16] Results obtained from the SABS show that the composition of Aspen Teicoplanin® and that of the innovator drug, Targocid®, are very similar (Table 2). Although some differences between the composition of the two teicoplanin preparations may exist, both preparations meet the *European Pharmacopoeia* requirements for a pharmaceutical-grade teicoplanin preparation.[16]

It has been argued that small variations in the relative abundance of the individual teicoplanin $A_2$ members could affect the overall efficacy of the drug.[12] This argument is based on minor differences between the lipophilicity of the various $A_2$ group members. Lipophilicity can play a major role in the pharmacokinetic profile of a drug because it can affect the distribution, binding affinities and elimination properties of the drug. Based on this, it was postulated that a teicoplanin preparation with a lower proportional content of subcomponents that have a longer half-life, like $A_{2-4}$ and $A_{2-5}$, and a higher proportion of those with a shorter half-life, like $A_{2-1}$ and $A_{2-2}$, would have more rapid overall elimination, and the resulting AUC would be decreased.[12] If this is the case, the opposite would also be true, i.e. that a preparation that contains more of the hydrophilic constituents would reach steady-state concentration faster. This would be a major advantage in a critically ill patient. However, previous research shows that none of these assumptions bear any clinical significance.

Bernareggi et al.[22] followed the pharmacokinetics of the individual teicoplanin components in man following intraveneous administration, and reported some differences between them. However, the authors of the manuscript themselves concluded that, overall, the differences among the individual components were relatively small, and that teicoplanin can be regarded as a single substance for clinical purposes.[22] A later study, in which the focus was also on individual teicoplanin components in man, utilised population pharmacokinetic modelling on data from 31 patients, and reached the same conclusion, i.e. that there was no clinically significant difference between the individual teicoplanin components in man.[23] These studies support the observations made in the present study.

## Conclusion

This study provides evidence that the composition of Aspen Teicoplanin® is similar to that of the innovator drug, Targocid®, and meets the requirements set out in the *European Pharmacopoeia*. The loading and maintenance schedules used in this study established therapeutic serum teicoplanin concentrations in critically ill patients. Evidence of bactericidal activity measured in patients' ex vivo serum samples, following treatment with the generic preparation, supports this finding.

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## References

1. Rothe C, Schlaich C, Thompson S. Healthcare-associated infections in sub-Saharan Africa. J Hosp Infect. 2013;85(4):257–67. Available from: http://www.sciencedirect.com/science/article/pii/S0195670113003241
2. Nathwani D, Li JZ, Balan DA, et al. An economic evaluation of a European cohort from a multinational trial of linezolid versus teicoplanin in serious Gram-positive bacterial infections: the importance of treatment setting in evaluating treatment effects. Int J Antimicrob Agents. 2004;23:315–24. Available from: http://www.sciencedirect.com/science/article/pii/S0924857903004473
3. Brogden RN, Peters DH. Teicoplanin. Drugs. 1994;47(5):823–54. Available from: http://link.springer.com/article/10.2165/00003495-199447050-00008
4. Taurino C, Frattini L, Marcone GL, et al. Actinoplanes teichomyceticus ATCC 31121 as a cell factory for producing teicoplanin. Microb Cell Fact. 2011;10:82. Available from: http://www.microbialcellfactories.com/content/10/1/82
5. Wilson APR. Clinical Pharmacokinetics of Teicoplanin. Clin Pharmacokinet. 2000;39(3): 167–83. Available from: http://link.springer.com/article/10.2165%2F00003088-200039030-00001
6. Mimoz O, Rolland D, Adoun M, et al. Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia. Intensive Care Med. 2006;32(5):775–9. Available from: http://link.springer.com/article/10.1007%2Fs00134-006-0136-3
7. Roberts JA, Stove V, De Waele JJ, et al. Variability in protein binding of teicoplanin and achievement of therapeutic drug monitoring targets in critically ill patients: lessons from the DALI Study. Int J Antimicrob Agents. 2014;43(5):423–30. Available from: http://www.ijaaonline.com/article/S0924-8579(14)00048-X/abstract
8. Matsumoto K, Kanazawa N, Fukamizu T, et al. Determination of teicoplanin trough concentration target and appropriate total dose during the first 3 days: a retrospective study in patients with MRSA infections. J Infect Chemother. 2010;16:193–9. Available from: http://www.sciencedirect.com/science/article/pii/S1341321X10706012
9. Grüneberg RN, Hryniewicz W. Clinical relevance of a European collaborative study on comparative susceptibility of Gram-positive clinical isolates to teicoplanin and vancomycin. Int J Antimicrob Agents. 1998;10(4):271–7. Available from: http://www.sciencedirect.com/science/article/pii/S0924857998000508
10. Abad F, Calbo F, Zapater P, et al. Comparative pharmacoeconomic study of vancomycin and teicoplanin in intensive care patients. Int J Antimicrob Agents. 2000;15:65–71. Available from: http://www.sciencedirect.com/science/article/pii/S0924857900001230
11. Chang HJ, Hsu PC, Yang CC, et al. Influence of teicoplanin MICs on treatment outcomes among patients with teicoplanin-treated meth-

icillin-resistant *Staphylococcus aureus* bacteraemia: a hospital-based retrospective study. J Antimicrob Chemother. 2012;67(3):736–41. Available from: http://jac.oxfordjournals.org/content/67/3/736.full.pdf
12. Brink AJ, Richards GA, Colombo G, et al. Multicomponent antibiotic substances produced by fermentation: implications for regulatory authorities, critically ill patients and generics. Int J Antimicrob Agents. 2014;43(1):1–6. Available from: http://www.sciencedirect.com/science/article/pii/S0924857913003367
13. Fung FH, Tang JC, Hopkins JP, et al. Measurement of teicoplanin by liquid chromatography-tandem mass spectrometry: development of a novel method. Ann Clin Biochem. 2012;49(5):475–81. Available from: http://acb.sagepub.com/content/49/5/475.abstract
14. Tisdale JE, Pasko MT, Mylotte JM. Antipseudomonal activity of simulated infusions of gentamicin alone or with piperacillin assessed by serum bactericidal rate and area under the killing curve. Antimicrob Agents Chemother. 1989;33(9):1500–5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC172690/
15. Clinical and Laboratory Standards Institute. Methods for determining bactericidal activity of antimicrobial agents (Approved Guideline M26-A). Wayne, PA: Clinical and Laboratory Standards Institute; 1999.
16. European Directorate for the Quality of Medicines and Healthcare (EDQM). European Pharmacopoeia. 8th ed. (volumes 8.0–8.2) Suppl 8.1; 2013; English version ISBN/ISSN: 978-92-871-7531-1.
17. Wang JT, Liao HI, Wu Lin FL, et al. Loading dose required to achieve rapid therapeutic teicoplanin trough plasma concentration in patients with multidrug-resistant gram-positive infections. Basic Clin Pharmacol Toxicol. 2012;110(5):416–20. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1742-7843.2012.00862.x/abstract;jsessionid=C81AA6B6D135625F7E4232675A1A83BD.f04t03
18. Seki M, Yabuno K, Miyawaki K, et al. Loading regimen required to rapidly achieve therapeutic trough plasma concentration of teicoplanin and evaluation of clinical features. Clin Pharmacol. 2012;4:71–5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3516451/
19. Ueda T, Takesue Y, Nakajima K, et al. Evaluation of teicoplanin dosing designs to achieve a new target trough concentration. J Infect Chemother. 2012;18(3):296–302. Available from: http://www.sciencedirect.com/science/article/pii/S1341321X12702970
20. Janknegt R. Teicoplanin in perspective. Pharm Weekbl Sci. 1991;13(4):153–60. Available from: http://link.springer.com/article/10.1007/BF01957739
21. Seki M, Yabuno K, Miyawaki K, et al. Loading regimen required to rapidly achieve therapeutic trough plasma concentration of teicoplanin and evaluation of clinical features. Clin Pharmacol. 2012;4:71–5. Available from: http://www.dovepress.com/loading-regimen-required-to-rapidly-achieve-therapeutic-trough-plasma--peer-reviewed-article-CPAA
22. Bernareggi A, Danese A, Cometti A, et al. Pharmacokinetics of individual components of teicoplanin in man. J Pharmacokinet Biopharm. 1990;18(6):525–43. Available from: http://link.springer.com/article/10.1007/BF01073937
23. Hanada K, Ikari S, Koukaki Y, et al. Comparison of pharmacokinetics of individual teicoplanin components in patients. Biol Pharm Bull. 2007;30(5):952–4. Available from: https://www.jstage.jst.go.jp/article/bpb/30/5/30_5_952/_article

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