PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT
DAPTOMYCIN – TRIMA 500 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Powder for solution for injection/infusion. Each vial contains 500 mg daptomycin as a sterile, lyophilized cake or powder.

1 INDICATIONS AND USAGE

DAPTOMYCIN – TRIMA 500 mg is indicated for the treatment of the infections listed below.

1.1 Complicated Skin and Skin Structure Infections

Complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis,* and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

1.2 *Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates

Staphylococcus aureus bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram negative or anaerobic organism.

1.3 Limitations of Use

DAPTOMYCIN – TRIMA 500 mg is not indicated for the treatment of pneumonia.

DAPTOMYCIN – TRIMA 500 mg is not indicated for the treatment of left-sided infective endocarditis due to *S. aureus*. The clinical trial of daptomycin in adult patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor *[see Clinical Studies (14.2)]*. Daptomycin has not been studied in patients with prosthetic valve endocarditis.

1.4 Usage

Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **DAPTOMYCIN – TRIMA 500 mg** and other antibacterial drugs, **DAPTOMYCIN – TRIMA 500 mg** should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

When culture and susceptibility information is available, it should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Empiric therapy may be initiated while awaiting test results.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Duration Instructions

Administer the appropriate volume of the reconstituted **DAPTOMYCIN – TRIMA 500 mg** (concentration of 50 mg/ml) intravenously either by injection over a two (2) minute period or by intravenous infusion over a thirty (30) minute period *[see Dosage and Administration (2.2, 2.3, 2.5)]*.

2.2 Dosage for Complicated Skin and Skin Structure Infections

Administer **DAPTOMYCIN – TRIMA 500 mg** 4 mg/kg intravenously in 0.9% sodium chloride injection once every 24 hours for 7 to 14 days.

2.3 Dosage in Patients with *Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin- Susceptible and Methicillin-Resistant Isolates

Administer **DAPTOMYCIN – TRIMA 500 mg** 6 mg/kg intravenously in 0.9% sodium chloride injection once every 24 hours for 2 to 6 weeks. There are limited safety data for the use of daptomycin for more than 28 days of therapy. In the Phase 3 trial, there were a total of 14 adult patients who were treated with daptomycin for more than 28 days.

2.4 Dosage in Patients with Renal Impairment

No dosage adjustment is required in adult patients with creatinine clearance (CL_{CR}) greater than or equal to 30 ml/min. The recommended dosage regimen for **DAPTOMYCIN – TRIMA 500 mg** in adult patients with CL_{CR} less than 30 mL/min, including adult patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), is 4 mg/kg (cSSSI) or 6 mg/kg (*S. aureus* bloodstream infections) once every 48 hours (Table 1). When possible, **DAPTOMYCIN – TRIMA 500 mg** should be administered following the completion of hemodialysis, on hemodialysis days *[see Warnings and Precautions (5.2, 5.10), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Table 1: Recommended Dosage of DAPTOMYCIN – TRIMA 500 mg in Adult Patients

Creatinine Clearance (CL_{CR})	Dosage Regimen	
	cSSSI	*S. aureus* Bloodstream Infections
Greater than or equal to 30 ml/min	4 mg/kg once every 24 hours	6 mg/kg once every 24 hours
Less than 30 ml/min, including hemodialysis and CAPD	4 mg/kg once every 48 hours*	6 mg/kg once every 48 hours*

* When possible, administer **DAPTOMYCIN – TRIMA 500 mg** following the completion of hemodialysis, on hemodialysis days.

2.5 Preparation and Administration of DAPTOMYCIN – TRIMA 500 mg

DAPTOMYCIN – TRIMA 500 mg is supplied in single-dose vials, each containing 500 mg daptomycin as a sterile, lyophilized cake or powder.
Daptomycin is given as 30-minute intravenous infusion.

A 50 mg/ml concentration of **DAPTOMYCIN – TRIMA 500 mg** powder for solution for injection/infusion is obtained by reconstituting the lyophilized product with 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection.
The lyophilized product takes approximately 15 minutes to dissolve. The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.
To prepare daptomycin for intravenous infusion, please adhere to the following instructions:
Aseptic technique should be used throughout to reconstitute or dilute lyophilized daptomycin.

For Reconstitution:
1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface. Draw 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device, then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial.
2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution. Vigorous shaking/agitation should be avoided to prevent foaming of the product.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of **DAPTOMYCIN – TRIMA 500 mg** range in colour from pale yellow to light brown.
5. The reconstituted solution should then be diluted with sodium chloride 9 mg/ml (0.9%) (typical volume 50 ml).

For Dilution:
1. Slowly remove the appropriate reconstituted liquid (50 mg daptomycin/ml) from the vial using a sterile needle that is 21 gauge or smaller in diameter by inverting the vial in order to allow the solution to drain towards the stopper. Using a syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove the required solution from the inverted vial.
2. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
3. Transfer the required reconstituted dose into 50 ml sodium chloride 9 mg/ml (0.9%).
4. The reconstituted and diluted solution should then be infused intravenously over 30 minutes.

DAPTOMYCIN – TRIMA 500 mg given as 2-minute intravenous injection (adult patients only)

Water should not be used for reconstitution of **DAPTOMYCIN – TRIMA 500 mg** for intravenous injection. **DAPTOMYCIN – TRIMA 500 mg** should only be reconstituted with sodium chloride 9 mg/ml (0.9%).

A 50 mg/ml concentration of **DAPTOMYCIN – TRIMA 500 mg** powder for solution for injection/infusion is obtained by reconstituting the lyophilized product with 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection.

The lyophilized product takes approximately 15 minutes to dissolve. The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.

To prepare **DAPTOMYCIN – TRIMA 500 mg** for intravenous injection, please adhere to the following instructions:

Aseptic technique should be used throughout to reconstitute lyophilized **DAPTOMYCIN – TRIMA 500 mg**.
1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface. Draw 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device, then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial.
2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution. Vigorous shaking/agitation should be avoided to prevent foaming of the product.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of **DAPTOMYCIN – TRIMA 500 mg** range in colour from pale yellow to light brown.
5. Slowly remove the reconstituted liquid (50 mg daptomycin/ml) from the vial using a sterile needle that is 21 gauge or smaller in diameter.
6. Invert the vial in order to allow the solution to drain towards the stopper. Using a new syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
7. Replace needle with a new needle for the intravenous injection.
8. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
9. The reconstituted solution should then be injected intravenously slowly over 2 minutes.

DAPTOMYCIN – TRIMA 500 mg vials are for single-use only.
From a microbiological point of view, the product should be used immediately after reconstitution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution. Do not exceed the In-Use storage conditions of the reconstituted and diluted solutions of **DAPTOMYCIN – TRIMA 500 mg** described below. Discard unused portions of **DAPTOMYCIN – TRIMA 500 mg.**

In-Use Storage Conditions for **DAPTOMYCIN – TRIMA 500 mg**
Once Reconstituted in Acceptable Intravenous Diluents

Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours at 2°C – 8°C.
For the 2-minute intravenous injection, the storage time of the reconstituted solution in the vial at 25°C must not exceed 12 hours (or 48 at 2°C – 8°C).

However, from a microbiological point of view the product should be used immediately. No preservative or bacteriostatic agent is present in this product. If not used immediately, in-use storage times are the responsibility of the user and would not normally be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical stability of the diluted solution in infusion bags is established as 12 hours at 25°C or 24 hours at 2°C-8°C. For the 30-minute intravenous infusion, the combined storage time (reconstituted solution in vial and diluted solution in infusion bag at 25°C must not exceed 12 hours (or 24 hours at 2°C - 8°C).

However, from a microbiological point of view the product should be used immediately. No preservative or bacteriostatic agent is present in this product. If not used immediately, in-use storage times are the responsibility of the user and would not normally be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

2.6 Compatible Intravenous Solution for Reconstitution and Dilution

DAPTOMYCIN – TRIMA 500 mg is compatible with 0.9% sodium chloride injection for reconstitution. Reconstituted **DAPTOMYCIN – TRIMA 500 mg** can only be diluted with 0.9% sodium chloride injection.

2.7 Incompatibilities

Daptomycin is not physically or chemically compatible with glucose-containing solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 2.5.

DAPTOMYCIN – TRIMA 500 mg should not be used in conjunction with ReadyMED® elastomeric infusion pumps. Stability studies of daptomycin solutions stored in ReadyMED® elastomeric infusion pumps identified an impurity (2-mercaptobenzothiazole) leaching from this pump system into the daptomycin solution.
Because only limited data are available on the compatibility of daptomycin with other IV substances, additives and other medications should not be added to **DAPTOMYCIN – TRIMA 500 mg** single-dose vials or infusion bags, or infused simultaneously with **DAPTOMYCIN – TRIMA 500 mg** through the same IV line. If the same IV line is used for sequential infusion of different drugs, the line should be flushed with a compatible intravenous solution before and after infusion with **DAPTOMYCIN – TRIMA 500 mg.**

3 DOSAGE FORMS AND STRENGTHS

For Injection/infusion: 500 mg daptomycin as a sterile, pale yellow to light brown lyophilized cake or powder for reconstitution in a single-dose vial.

4 CONTRAINDICATIONS

DAPTOMYCIN – TRIMA 500 mg is contraindicated in patients with known hypersensitivity to daptomycin *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis/Hypersensitivity Reactions

Anaphylaxis/hypersensitivity reactions have been reported with the use of antibacterial agents, including daptomycin, and may be life-threatening. If an allergic reaction to **DAPTOMYCIN – TRIMA 500 mg** occurs, discontinue the drug and institute appropriate therapy *[see Adverse Reactions (6.2)]*.

5.2 Myopathy and Rhabdomyolysis

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal (ULN), has been reported with the use of daptomycin. Rhabdomyolysis, with or without acute renal failure, has been reported *[see Adverse Reactions (6.2)]*.

Patients receiving **DAPTOMYCIN – TRIMA 500 mg** should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive **DAPTOMYCIN – TRIMA 500 mg,** CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor or in whom elevations in CPK occur during treatment with **DAPTOMYCIN – TRIMA 500 mg**.

In adult patients with renal impairment, both renal function and CPK should be monitored more frequently than once weekly *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

In Phase 1 studies and Phase 2 clinical trials in adults, CPK elevations appeared to be more frequent when daptomycin was dosed more than once daily. Therefore, **DAPTOMYCIN – TRIMA 500 mg** should not be dosed more frequently than once a day.

DAPTOMYCIN – TRIMA 500 mg should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevations to levels >1,000 U/L (~5× ULN), and in patients without reported symptoms who have marked elevations in CPK, with levels >2,000 U/L (≥10× ULN).

In addition, consideration should be given to suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, temporarily in patients receiving **DAPTOMYCIN – TRIMA 500 mg** *[see Drug Interactions (7.1)]*.

5.3 Eosinophilic Pneumonia

Eosinophilic pneumonia has been reported in patients receiving daptomycin *[see Adverse Reactions (6.2)]*. In reported cases associated with daptomycin, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organizing pneumonia. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting daptomycin and improved when daptomycin was discontinued and steroid therapy was initiated. Recurrence of eosinophilic pneumonia upon re- exposure has been reported. Patients who develop these signs and symptoms while receiving **DAPTOMYCIN – TRIMA 500 mg** should undergo prompt medical evaluation, and **DAPTOMYCIN – TRIMA 500 mg** should be discontinued immediately. Treatment with systemic steroids is recommended.

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS has been reported in post-marketing experience with daptomycin *[see Adverse Reactions (6.2)]*. Patients who develop skin rash, fever, peripheral eosinophilia, and systemic organ (for example, hepatic, renal, pulmonary) impairment while receiving **DAPTOMYCIN – TRIMA 500 mg** should undergo medical evaluation. If DRESS is suspected, discontinue **DAPTOMYCIN – TRIMA 500 mg** promptly and institute appropriate treatment.

5.5 Tubulointerstitial Nephritis (TIN)

TIN has been reported in post-marketing experience with daptomycin *[see Adverse Reactions (6.2)]*. Patients who develop new or worsening renal impairment while receiving **DAPTOMYCIN – TRIMA 500 mg** should undergo medical evaluation. If TIN is suspected, discontinue **DAPTOMYCIN – TRIMA 500 mg** promptly and institute appropriate treatment.

5.6 Peripheral Neuropathy

Cases of peripheral neuropathy have been reported during the daptomycin post marketing experience *[see Adverse Reactions (6.2)]*. Therefore, physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving **DAPTOMYCIN – TRIMA 500 mg.** Monitor for neuropathy and consider discontinuation.

5.7 Potential Nervous System and/or Muscular System Effects in Pediatric Patients Younger than 12 Months

Avoid use of **DAPTOMYCIN – TRIMA 500 mg** in pediatric patients younger than 12 months due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs with intravenous daptomycin *[see Nonclinical Toxicology (13.2)]*.

5.8 *Clostridioides difficile*–Associated Diarrhea

Clostridioides difficile–associated diarrhea (CDAD) has been reported with the use of nearly all systemic antibacterial agents, including daptomycin, and may range in severity from mild diarrhea to fatal colitis *[see Adverse Reactions (6.2)]*. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin- producing strains of *C. difficile* cause increased morbidity and mortality, since these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.9 Persisting or Relapsing *S. aureus* Bacteremia/Endocarditis

Patients with persisting or relapsing *S. aureus* bacteremia/endocarditis or poor clinical response should have repeat blood cultures. If a blood culture is positive for *S. aureus*, minimum inhibitory concentration (MIC) susceptibility testing of the isolate should be performed using a standardized procedure, and diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection.
Appropriate surgical intervention (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibacterial regimen may be required.

Failure of treatment due to persisting or relapsing *S. aureus* bacteremia/endocarditis may be due to reduced daptomycin susceptibility (as evidenced by increasing MIC of the *S. aureus* isolate) *[see Clinical Studies (14.2)]*.

5.10 Decreased Efficacy in Patients with Moderate Baseline Renal Impairment

Limited data are available from the two Phase 3 complicated skin and skin structure infection (cSSSI) trials regarding clinical efficacy of daptomycin treatment in adult patients with creatinine clearance (CL_{CR}) <50 ml/min; only 31/534 (6%) patients treated with daptomycin in the intent-to-treat (ITT) population had a baseline CL_{CR} <50 ml/min. Table 2 shows the number of adult patients by renal function and treatment group who were clinical successes in the Phase 3 cSSSI trials.

Table 2: Clinical Success Rates by Renal Function and Treatment Group in Phase 3 cSSSI Trials in Adult Patients (Population: ITT)

CL_{CR}	Success Rate n/N (%)	
	Daptomycin 4 mg/kg every 24h	Comparator
50–70 ml/min	25/38 (66%)	30/48 (63%)
30–<50 ml/min	7/15 (47%)	20/35 (57%)

In a subgroup analysis of the ITT population in the Phase 3 *S. aureus* bacteremia/endocarditis trial, clinical success rates, as determined by a treatment-blinded Adjudication Committee *[see Clinical Studies (14.2)]*, in the daptomycin -treated adult patients were lower in patients with baseline CL_{CR} <50 ml/min (see Table 3). A decrease of the magnitude shown in Table 3 was not observed in comparator-treated patients.

Table 3: Adjudication Committee Clinical Success Rates at Test of Cure by Baseline Creatinine Clearance and Treatment Subgroup in the *S. aureus* Bacteremia/Endocarditis Trial in Adult Patients (Population: ITT)

Baseline CL_{CR}	Success Rate n/N (%)			
	Daptomycin 6 mg/kg every 24h		Comparator	
	Bacteremia	Right-Sided Infective Endocarditis	Bacteremia	Right-Sided Infective Endocarditis
>80 ml/min	30/50 (60%)	7/14 (50%)	19/42 (45%)	5/11 (46%)
50–80 ml/min	12/26 (46%)	1/4 (25%)	13/31 (42%)	1/2 (50%)
30–<50 ml/min	2/14 (14%)	0/1 (0%)	7/17 (41%)	1/1 (100%)

Consider these data when selecting antibacterial therapy for use in adult patients with baseline moderate to severe renal impairment.

5.11 Increased International Normalized Ratio (INR)/Prolonged Prothrombin Time

Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay *[see Drug Interactions (7.2)]*.

5.12 Development of Drug-Resistant Bacteria

Prescribing **DAPTOMYCIN – TRIMA 500 mg** in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:
- Anaphylaxis/Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Myopathy and Rhabdomyolysis *[see Warnings and Precautions (5.2)]*
- Eosinophilic Pneumonia *[see Warnings and Precautions (5.3)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms *[see Warnings and Precautions (5.4)]*
- Tubulointerstitial Nephritis *[see Warnings and Precautions (5.5)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.6)]*
- Increased International Normalized Ratio (INR)/Prolonged Prothrombin Time *[see Warnings and Precautions (5.11) and Drug Interactions (7.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical trials enrolled 1,864 adult patients treated with daptomycin and 1,416 treated with comparator.

Complicated Skin and Skin Structure Infection Trials in Adults

In Phase 3 complicated skin and skin structure infection (cSSSI) trials in adult patients, daptomycin was discontinued in 15/534 (2.8%) patients due to an adverse reaction, while comparator was discontinued in 17/558 (3.0%) patients.

The rates of the most common adverse reactions, organized by body system, observed in adult patients with cSSSI (receiving 4 mg/kg daptomycin) are displayed in Table 4.

Table 4: Incidence of Adverse Reactions that Occurred in ≥2% of Adult Patients in the Daptomycin Treatment Group and ≥ the Comparator Treatment Group in Phase 3 cSSSI Trials

Adverse Reaction	Adult Patients (%)	
	Daptomycin 4 mg/kg (N=534)	Comparator* (N=558)
Gastrointestinal disorders		
Diarrhea	5.2	4.3
Nervous system disorders		
Headache	5.4	5.4
Dizziness	2.2	2.0
Skin/subcutaneous disorders		
Rash	4.3	3.8
Diagnostic investigations		
Abnormal liver function tests	3.0	1.6
Elevated CPK	2.8	1.8
Infections		
Urinary tract infections	2.4	0.5
Vascular disorders		
Hypotension	2.4	1.4
Respiratory disorders		
Dyspnea	2.1	1.6

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

Drug-related adverse reactions (possibly or probably drug-related) that occurred in <1% of adult patients receiving daptomycin in the cSSSI trials are as follows:

Body as a Whole: fatigue, weakness, rigors, flushing, hypersensitivity

Blood/Lymphatic System: leukocytosis, thrombocytopenia, thrombocytosis, eosinophilia, increased International Normalized Ratio (INR)

Cardiovascular System: supraventricular arrhythmia

Dermatologic System: eczema

Digestive System: abdominal distension, stomatitis, jaundice, increased serum lactate dehydrogenase

Metabolic/Nutritional System: hypomagnesemia, increased serum bicarbonate, electrolyte disturbance

Musculoskeletal System: myalgia, muscle cramps, muscle weakness, arthralgia

Nervous System: vertigo, mental status change, paresthesia

Special Senses: taste disturbance, eye irritation

S. aureus Bacteremia/Endocarditis Trial in Adults

In the *S. aureus* bacteremia/endocarditis trial involving adult patients, daptomycin was discontinued in 20/120 (16.7%) patients due to an adverse reaction, while comparator was discontinued in 21/116 (18.1%) patients.

Serious Gram-negative infections (including bloodstream infections) were reported in 10/120 (8.3%) daptomycin-treated patients and 0/115 comparator-treated patients. Comparator-treated patients received dual therapy that included initial gentamicin for 4 days. Infections were reported during treatment and during early and late follow-up. Gram-negative infections included cholangitis, alcoholic pancreatitis, sternal osteomyelitis/mediastinitis, bowel infarction, recurrent Crohn's disease, recurrent line sepsis, and recurrent urosepsis caused by a number of different Gram-negative bacteria.

The rates of the most common adverse reactions, organized by System Organ Class (SOC), observed in adult patients with *S. aureus* bacteremia/endocarditis (receiving 6 mg/kg daptomycin) are displayed in Table 5.

Table 5: Incidence of Adverse Reactions that Occurred in ≥5% of Adult Patients in the Daptomycin Treatment Group and ≥ the Comparator Treatment Group in the *S. aureus* Bacteremia/Endocarditis Trial

Adverse Reaction*	Adult Patients n (%)	
	Daptomycin 6 mg/kg (N=120)	Comparator† (N=116)
Infections and infestations		
Sepsis NOS	6 (5%)	3 (3%)
Bacteremia	6 (5%)	0 (0%)
Gastrointestinal disorders		
Abdominal pain NOS	7 (6%)	4 (3%)
General disorders and administration site conditions		
Chest pain	8 (7%)	7 (6%)
Edema NOS	8 (7%)	5 (4%)
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	10 (8%)	2 (2%)
Skin and subcutaneous tissue disorders		
Pruritus	7 (6%)	6 (5%)
Sweating increased	6 (5%)	0 (0%)
Psychiatric disorders		
Insomnia	11 (9%)	8 (7%)
Investigations		
Blood creatine phosphokinase increased	8 (7%)	1 (1%)
Vascular disorders		
Hypertension NOS	7 (6%)	3 (3%)

* NOS, not otherwise specified.
† Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.

The following reactions, not included above, were reported as possibly or probably drug-related in the daptomycin-treated group:

Blood and Lymphatic System Disorders: eosinophilia, lymphadenopathy, thrombocythemia, thrombocytopenia

Cardiac Disorders: atrial fibrillation, atrial flutter, cardiac arrest

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: vision blurred

Gastrointestinal Disorders: dry mouth, epigastric discomfort, gingival pain, hypoesthesia oral

Infections and Infestations: candidal infection NOS, vaginal candidiasis, fungemia, oral candidiasis, urinary tract infection fungal

Investigations: blood phosphorous increased, blood alkaline phosphatase increased, INR increased, liver function test abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, prothrombin time prolonged

Metabolism and Nutrition Disorders: appetite decreased NOS

Musculoskeletal and Connective Tissue Disorders: myalgia

Nervous System Disorders: dyskinesia, paresthesia *Psychiatric Disorders:* hallucination NOS

Renal and Urinary Disorders: proteinuria, renal impairment NOS

Skin and Subcutaneous Tissue Disorders: pruritus generalized, rash vesicular

Other Trials in Adults

In Phase 3 trials of community-acquired pneumonia (CAP) in adult patients, the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events *[see Indications and Usage (1.3)]*.

Laboratory Changes in Adults

Complicated Skin and Skin Structure Infection Trials in Adults
In Phase 3 cSSSI trials of adult patients receiving daptomycin at a dose of 4 mg/kg, elevations in CPK were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared with 10/558 (1.8%) comparator-treated patients. Of the 534 patients treated with daptomycin, 1 (0.2%) had symptoms of muscle pain or weakness associated with CPK elevations to greater than 4 times the upper limit of normal (ULN). The symptoms resolved within 3 days and CPK returned to normal within 7 to 10 days after treatment was discontinued *[see Warnings and Precautions (5.2)]*. Table 6 summarizes the CPK shifts from Baseline through End of Therapy in the cSSSI adult trials.

Table 6: Incidence of CPK Elevations from Baseline during Therapy in Either the Daptomycin Treatment Group or the Comparator Treatment Group in Phase 3 cSSSI Adult Trials

Change in CPK		All Adult Patients				Adult Patients with Normal CPK at Baseline			
		Daptomycin 4 mg/kg (N=430)		Comparator* (N=459)		Daptomycin 4 mg/kg (N=374)		Comparator* (N=392)	
		%	n	%	n	%	n	%	n
No Increase		90.7	390	91.1	418	91.2	341	91.1	357
Maximum Value	>1×ULN†	9.3	40	8.9	41	8.8	33	8.9	35
	>2×ULN	4.9	21	4.8	22	3.7	14	3.1	12
	>4×ULN	1.4	6	1.5	7	1.1	4	1.0	4
	>5×ULN	1.4	6	0.4	2	1.1	4	0.0	0
	>10×ULN	0.5	2	0.2	1	0.2	1	0.0	0

Note: Elevations in CPK observed in adult patients treated with daptomycin or comparator were not clinically or statistically significantly different.
* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).
†ULN (Upper Limit of Normal) is defined as 200 U/L.

S. aureus Bacteremia/Endocarditis Trial in Adults
In the *S. aureus* bacteremia/endocarditis trial in adult patients, at a dose of 6 mg/kg, 11/120 (9.2%) daptomycin-treated patients, including two patients with baseline CPK levels >500 U/L, had CPK elevations to levels >500 U/L, compared with 1/116 (0.9%) comparator-treated patients. Of the 11 daptomycin-treated patients, 4 had prior or concomitant treatment with an HMG-CoA reductase inhibitor. Three of these 11 daptomycin-treated patients discontinued therapy due to CPK elevation, while the one comparator-treated patient did not discontinue therapy *[see Warnings and Precautions (5.2)]*.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of daptomycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: anemia, thrombocytopenia

General and administration site conditions: pyrexia

Immune System Disorders: anaphylaxis; hypersensitivity reactions, including angioedema, pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema, and pulmonary eosinophilia *[see Contraindications (4) and Warnings and Precautions (5.1)]*

Infections and Infestations: Clostridioides difficile–associated diarrhea *[see Warnings and Precautions (5.8)]*

Laboratory Investigations: platelet count decreased

Musculoskeletal Disorders: myoglobin increased; rhabdomyolysis (some reports involved patients treated concurrently with daptomycin and HMG-CoA reductase inhibitors) *[see Warnings and Precautions (5.2), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*

Respiratory, Thoracic, and Mediastinal Disorders: cough, eosinophilic pneumonia, organizing pneumonia *[see Warnings and Precautions (5.3)]*

Nervous System Disorders: peripheral neuropathy *[see Warnings and Precautions (5.6)]*

Skin and Subcutaneous Tissue Disorders: serious skin reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS), vesiculobullous rash (with or without mucous membrane involvement, including Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]), and acute generalized exanthematous pustulosis *[see Warnings and Precautions (5.4)]*

Gastrointestinal Disorders: nausea, vomiting

Renal and urinary disorders: acute kidney injury, renal insufficiency, renal failure, and tubulointerstitial nephritis (TIN) *[see Warnings and Precautions (5.5)]*

Special Senses: visual disturbances

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
Also, you can report to safety@trima.co.il

7 DRUG INTERACTIONS

7.1 HMG-CoA Reductase Inhibitors

In healthy adult subjects, concomitant administration of daptomycin and simvastatin had no effect on plasma trough concentrations of simvastatin, and there were no reports of skeletal myopathy *[see Clinical Pharmacology (12.3)]*.

However, inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of creatine phosphokinase (CPK). In the adult Phase 3 *S. aureus* bacteremia/endocarditis trial, some patients who received prior or concomitant treatment with an HMG-CoA reductase inhibitor developed elevated CPK *[see Adverse Reactions (6.1)]*. Experience with the coadministration of HMG-CoA reductase inhibitors and daptomycin in patients is limited; therefore, consideration should be given to suspending use of HMG-CoA reductase inhibitors temporarily in patients receiving daptomycin.

7.2 Drug-Laboratory Test Interactions

Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay. The possibility of an erroneously elevated PT/INR result due to interaction with a recombinant thromboplastin reagent may be minimized by drawing specimens for PT or INR testing near the time of trough plasma concentrations of daptomycin. However, sufficient daptomycin concentrations may be present at trough to cause interaction.

If confronted with an abnormally high PT/INR result in a patient being treated with **DAPTOMYCIN – TRIMA 500 mg,** it is recommended that clinicians:
1. Repeat the assessment of PT/INR, requesting that the specimen be drawn just prior to the next **DAPTOMYCIN – TRIMA 500 mg** dose (i.e., at trough concentration). If the PT/INR value obtained at trough remains substantially elevated above what would otherwise be expected, consider evaluating PT/INR utilizing an alternative method.
2. Evaluate for other causes of abnormally elevated PT/INR results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on use of daptomycin in pregnant women are insufficient to inform a drug- associated risk for major birth defects and miscarriage. In animal reproduction studies performed in rats and rabbits daptomycin was administered intravenously during organogenesis at doses 2 and 4- times, respectively, the recommended 6 mg/kg human dose (on a body surface area basis). No evidence of adverse developmental outcomes was observed.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data
In pregnant rats, daptomycin was administered intravenously at doses of 5, 20, or 75 mg/kg/day during the gestation days 6 to 18. Maternal body weight gain was decreased at 75 mg/kg/day. No embryo/fetal effects were noted at the highest dose of 75 mg/kg/day, a dose approximately 2-fold higher than in humans at the recommended maximum dose of 6mg/kg (based on body surface area).

In pregnant rabbits, daptomycin was administered intravenously at doses of 5, 20, or 75 mg/kg/day during the gestation days 6 to 15. Maternal body weight gain and food consumption were decreased at 75 mg/kg/day. No embryo/fetal effects were noted at the highest dose of 75 mg/kg/day, a dose approximately 4-fold higher than in humans at the maximum recommended dose of 6mg/kg (based on body surface area).

In a combined fertility and pre/postnatal development study, daptomycin was administered intravenously to female rats at doses of 2, 25, 75 mg/kg/day from 14-days pre-mating through lactation/postpartum day 20. No effects on pre/postnatal development were observed up to the highest dose of 75 mg/kg/day, a dose approximately 2-fold higher than the maximum recommended human dose of 6 mg/kg (based on body surface area)[1].

Daptomycin - Trima 500 mg
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8.2 Lactation

Risk Summary

Limited published data report that daptomycin is present in human milk at infant doses of 0.1% of the maternal dose *(see Data)*[2,3,4]. There is no information on the effects of daptomycin on the breastfed infant or the effects of daptomycin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **DAPTOMYCIN – TRIMA 500 mg** and any potential adverse effects on the breastfed infant from **DAPTOMYCIN – TRIMA 500 mg** or from the underlying maternal condition.

8.4 Pediatric Use

DAPTOMYCIN – TRIMA 500 mg is not indicated for children and adolescents under 18 years of age.

8.5 Geriatric Use

Of the 534 adult patients treated with daptomycin in Phase 3 controlled clinical trials of complicated skin and skin structure infections (cSSSI), 27% were 65 years of age or older and 12% were 75 years of age or older. Of the 120 adult patients treated with daptomycin in the Phase 3 controlled clinical trial of *S. aureus* bacteremia/endocarditis, 25% were 65 years of age or older and 16% were 75 years of age or older. In Phase 3 adult clinical trials of cSSSI and *S. aureus* bacteremia/endocarditis, clinical success rates were lower in patients ≥65 years of age than in patients <65 years of age. In addition, treatment- emergent adverse events were more common in patients ≥65 years of age than in patients <65 years of age.

The exposure of daptomycin was higher in healthy elderly subjects than in healthy young adult subjects. However, no adjustment of **DAPTOMYCIN – TRIMA 500 mg** dosage is warranted for elderly patients with creatinine clearance (CL_{CR}) ≥30 ml/min *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

8.6 Patients with Renal Impairment

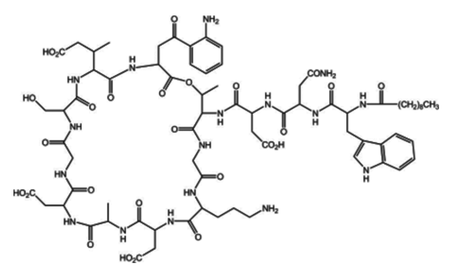
Daptomycin is eliminated primarily by the kidneys; therefore, a modification of **DAPTOMYCIN – TRIMA 500 mg** dosage interval is recommended for adult patients with CL_{CR} <30 ml/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). In adult patients with renal impairment, both renal function and creatine phosphokinase (CPK) should be monitored more frequently than once weekly *[see Dosage and Administration (2.4), Warnings and Precautions (5.2, 5.10), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is cleared slowly from the body by hemodialysis (approximately 15% of the administered dose is removed over 4 hours) and by peritoneal dialysis (approximately 11% of the administered dose is removed over 48 hours). The use of high-flux dialysis membranes during 4 hours of hemodialysis may increase the percentage of dose removed compared with that removed by low-flux membranes.

11 DESCRIPTION

DAPTOMYCIN – TRIMA 500 mg (daptomycin for injection/infusion) contains daptomycin, a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*. The chemical name is N-decanoyl-L-tryptophyl-D-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine ε₁-lactone. The chemical structure is:



The empirical formula is $C_{72}H_{101}N_{17}O_{26}$; the molecular weight is 1620.67. **DAPTOMYCIN – TRIMA 500 mg** is supplied in a single-dose vial as a sterile, preservative-free, pale yellow to light brown, lyophilized cake or powder containing approximately 500 mg of daptomycin for intravenous (IV) use following reconstitution with 0.9% sodium chloride injection *[see Dosage and Administration (2.5)]*. The only inactive ingredient is sodium hydroxide, and water for injection which is used for pH adjustment.
Following reconstitution: the solution of **DAPTOMYCIN – TRIMA 500 mg** is clear, pale yellow to light brown, free from visible extraneous matters.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Daptomycin is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

Based on animal models of infection, the antimicrobial activity of daptomycin appears to correlate with the AUC/MIC (area under the concentration-time curve/minimum inhibitory concentration) ratio for certain pathogens, including *S. aureus*. The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with daptomycin.

12.3 Pharmacokinetics

Daptomycin Administered over a 30-Minute Period in Adults

The mean and standard deviation (SD) pharmacokinetic parameters of daptomycin at steady-state following intravenous (IV) administration of daptomycin over a 30-minute period at 4 to 12 mg/kg every 24h to healthy young adults are summarized in Table 7.

Table 7: Mean (SD) Daptomycin Pharmacokinetic Parameters in Healthy Adult Volunteers at Steady-State

Dose*† (mg/kg)	Pharmacokinetic Parameters‡				
	AUC_{0-24} (mcg•h/ml)	$t_{1/2}$ (h)	V_{ss} (L/kg)	CL_T (ml/h/kg)	C_{max} (mcg/ml)
4 (N=6)	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	57.8 (3.0)
6 (N=6)	632 (78)	7.9 (1.0)	0.101 (0.007)	9.1 (1.5)	93.9 (6.0)
8 (N=6)	858 (213)	8.3 (2.2)	0.101 (0.013)	9.0 (3.0)	123.3 (16.0)
10 (N=9)	1039 (178)	7.9 (0.6)	0.098 (0.017)	8.8 (2.2)	141.1 (24.0)
12 (N=9)	1277 (253)	7.7 (1.1)	0.097 (0.018)	9.0 (2.8)	183.7 (25.0)

* Daptomycin was administered by IV infusion over a 30-minute period.
† Doses of daptomycin in excess of 6 mg/kg have not been approved.
‡ AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady-state; CL_T, total plasma clearance; C_{max}, maximum plasma concentration.

Daptomycin pharmacokinetics were generally linear and time-independent at daptomycin doses of 4 to 12 mg/kg every 24h administered by IV infusion over a 30-minute period for up to 14 days. Steady- state trough concentrations were achieved by the third daily dose. The mean (SD) steady-state trough concentrations attained following the administration of 4, 6, 8, 10, and 12 mg/kg every 24h were 5.9 (1.6), 6.7 (1.6), 10.3 (5.5), 12.9 (2.9), and 13.7 (5.2) mcg/ml, respectively.

Daptomycin Administered over a 2-Minute Period in Adults

Following IV administration of daptomycin over a 2-minute period to healthy adult volunteers at doses of 4 mg/kg (N=8) and 6 mg/kg (N=12), the mean (SD) steady-state systemic exposure (AUC) values were 475 (71) and 701 (82) mcg•h/ml, respectively. Values for maximum plasma concentration (C_{max}) at the end of the 2-minute period could not be determined adequately in this study. However, using pharmacokinetic parameters from 14 healthy adult volunteers who received a single dose of daptomycin 6 mg/kg IV administered over a 30-minute period in a separate study, steady-state C_{max} values were simulated for daptomycin 4 and 6 mg/kg IV administered over a 2-minute period. The simulated mean (SD) steady-state C_{max} values were 77.7 (8.1) and 116.6 (12.2) mcg/ml, respectively.

Distribution

Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The overall mean binding ranges from 90 to 93%.

In clinical studies, mean serum protein binding in adult subjects with creatinine clearance (CL_{CR}) ≥30 ml/min was comparable to that observed in healthy adult subjects with normal renal function. However, there was a trend toward decreasing serum protein binding among subjects with CL_{CR} <30 ml/min (88%), including those receiving hemodialysis (86%) and continuous ambulatory peritoneal dialysis (CAPD) (84%). The protein binding of daptomycin in adult subjects with moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy adult subjects.

The volume of distribution at steady-state (V_{ss}) of daptomycin in healthy adult subjects was approximately 0.1 L/kg and was independent of dose.

Metabolism

In *in vitro* studies, daptomycin was not metabolized by human liver microsomes.
In 5 healthy adults after infusion of radiolabeled ^{14}C-daptomycin, the plasma total radioactivity was similar to the concentration determined by microbiological assay. Inactive metabolites were detected in urine, as determined by the difference between total radioactive concentrations and microbiologically active concentrations. In a separate study, no metabolites were observed in plasma on Day 1 following the administration of daptomycin at 6 mg/kg to adult subjects. Minor amounts of three oxidative metabolites and one unidentified compound were detected in urine. The site of metabolism has not been identified.

Excretion

Daptomycin is excreted primarily by the kidneys. In a mass balance study of 5 healthy adult subjects using radiolabeled daptomycin, approximately 78% of the administered dose was recovered from urine based on total radioactivity (approximately 52% of the dose based on microbiologically active concentrations), and 5.7% of the administered dose was recovered from feces (collected for up to 9 days) based on total radioactivity.

Specific Populations

Patients with Renal Impairment

Population-derived pharmacokinetic parameters were determined for infected adult patients (complicated skin and skin structure infections [cSSSI] and *S. aureus* bacteremia) and noninfected adult subjects with various degrees of renal function (Table 8). Total plasma clearance (CL_T), elimination half-life ($t_{1/2}$), and volume of distribution at steady-state (V_{ss}) in patients with cSSSI were similar to those in patients with *S. aureus* bacteremia. Following administration of daptomycin 4 mg/kg every 24h by IV infusion over a 30-minute period, the mean CL_T was 9%, 22%, and 46% lower among subjects and patients with mild (CL_{CR} 50–80 ml/min), moderate (CL_{CR} 30–<50 ml/min), and severe (CL_{CR} <30 ml/min) renal impairment, respectively, than in those with normal renal function (CL_{CR} >80 ml/min). The mean steady-state systemic exposure (AUC), $t_{1/2}$, and V_{ss} increased with decreasing renal function, although the mean AUC for patients with CL_{CR} 30–80 ml/min was not markedly different from the mean AUC for patients with normal renal function. The mean AUC for patients with CL_{CR} <30 ml/min and for patients on dialysis (CAPD and hemodialysis dosed post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function. The mean C_{max} ranged from 60 to 70 mcg/ml in patients with CL_{CR} ≥30 ml/min, while the mean C_{max} for patients with CL_{CR} <30 ml/min ranged from 41 to 58 mcg/ml. After administration of daptomycin 6 mg/kg every 24h by IV infusion over a 30-minute period, the mean C_{max} ranged from 80 to 114 mcg/ml in patients with mild to moderate renal impairment and was similar to that of patients with normal renal function.

Table 8: Mean (SD) Daptomycin Population Pharmacokinetic Parameters Following Infusion of Daptomycin 4 mg/kg or 6 mg/kg to Infected Adult Patients and Noninfected Adult Subjects with Various Degrees of Renal Function

Renal Function	Pharmacokinetic Parameters*					
	$t_{1/2}$† (h) 4 mg/kg	V_{ss}† (L/kg) 4 mg/kg	CL_T† (ml/h/kg) 4 mg/kg	$AUC_{0-\infty}$† (mcg•h/ml) 4 mg/kg	AUC_{ss}‡ (mcg•h/ml) 6 mg/kg	$C_{min,ss}$‡ (mcg/ml) 6 mg/kg
Normal (CL_{CR} >80 ml/min)	9.39 (4.74) N=165	0.13 (0.05) N=165	10.9 (4.0) N=165	417 (155) N=165	545 (296) N=62	6.9 (3.5) N=61
Mild Renal Impairment (CL_{CR} 50–80 ml/min)	10.75 (8.36) N=64	0.12 (0.05) N=64	9.9 (4.0) N=64	466 (177) N=64	637 (215) N=29	12.4 (5.6) N=29
Moderate Renal Impairment (CL_{CR} 30–<50 ml/min)	14.70 (10.50) N=24	0.15 (0.06) N=24	8.5 (3.4) N=24	560 (258) N=24	868 (349) N=15	19.0 (9.0) N=14
Severe Renal Impairment (CL_{CR} <30 ml/min)	27.83 (14.85) N=8	0.20 (0.15) N=8	5.9 (3.9) N=8	925 (467) N=8	1050 (892) N=2	24.4 (21.4) N=2
Hemodialysis	30.51 (6.51) N=16	0.16 (0.04) N=16	3.9 (2.1) N=16	1193 (399) N=16	NA	NA
CAPD	27.56 (4.53) N=5	0.11 (0.02) N=5	2.9 (0.4) N=5	1409 (238) N=5	NA	NA

Note: daptomycin was administered over a 30-minute period.
* CL_{CR}, creatinine clearance estimated using the Cockcroft-Gault equation with actual body weight; CAPD, continuous ambulatory peritoneal dialysis; $AUC_{0-\infty}$, area under the concentration-time curve extrapolated to infinity; AUC_{ss}, area under the concentration-time curve calculated over the 24-hour dosing interval at steady-state; $C_{min,ss}$, trough concentration at steady-state; NA, not applicable.
† Parameters obtained following a single dose from patients with complicated skin and skin structure infections and healthy subjects.
‡ Parameters obtained at steady-state from patients with *S. aureus* bacteremia.

Because renal excretion is the primary route of elimination, adjustment of **DAPTOMYCIN – TRIMA 500 mg** dosage interval is necessary in adult patients with severe renal impairment (CL_{CR} <30 ml/min) *[see Dosage and Administration (2.4)]*.

Patients with Hepatic Impairment

The pharmacokinetics of daptomycin were evaluated in 10 adult subjects with moderate hepatic impairment (Child-Pugh Class B) and compared with those in healthy adult volunteers (N=9) matched for gender, age, and weight. The pharmacokinetics of daptomycin were not altered in subjects with moderate hepatic impairment. No dosage adjustment is warranted when **DAPTOMYCIN – TRIMA 500 mg** is administered to patients with mild to moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh Class C) have not been evaluated.

Gender

No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed. No dosage adjustment is warranted based on gender when **DAPTOMYCIN – TRIMA 500 mg** is administered.

Geriatric Patients

The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects (≥75 years of age) and 11 healthy young adult controls (18 to 30 years of age). Following administration of a single 4 mg/kg dose of daptomycin by IV infusion over a 30-minute period, the mean total clearance of daptomycin was approximately 35% lower and the mean $AUC_{0-\infty}$ was approximately 58% higher in elderly subjects than in healthy young adult subjects. There were no differences in C_{max} *[see Use in Specific Populations (8.5)]*.

Obese Patients

The pharmacokinetics of daptomycin were evaluated in 6 moderately obese (Body Mass Index [BMI] 25 to 39.9 kg/m²) and 6 extremely obese (BMI ≥40 kg/m²) adult subjects and controls matched for age, gender, and renal function. Following administration of daptomycin by IV infusion over a 30-minute period as a single 4 mg/kg dose based on total body weight, the total plasma clearance of daptomycin normalized to total body weight was approximately 15% lower in moderately obese subjects and 23% lower in extremely obese subjects than in nonobese controls. The $AUC_{0-\infty}$ of daptomycin was approximately 30% higher in moderately obese subjects and 31% higher in extremely obese subjects than in nonobese controls. The differences were most likely due to differences in the renal clearance of daptomycin. No adjustment of **DAPTOMYCIN – TRIMA 500 mg** dosage is warranted in obese patients.

Drug Interaction Studies

In Vitro Studies

In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of the following human cytochrome P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the P450 system.

Aztreonam

In a study in which 15 healthy adult subjects received a single dose of daptomycin 6 mg/kg IV and a combination dose of daptomycin 6 mg/kg IV and aztreonam 1 g IV, administered over a 30-minute period, the C_{max} and $AUC_{0-\infty}$ of daptomycin were not significantly altered by aztreonam.

Tobramycin

In a study in which 6 healthy adult males received a single dose of daptomycin 2 mg/kg IV, tobramycin 1 mg/kg IV, and both in combination, administered over a 30-minute period, the mean C_{max} and $AUC_{0-\infty}$ of daptomycin were 12.7% and 8.7% higher, respectively, when daptomycin was coadministered with tobramycin. The mean C_{max} and $AUC_{0-\infty}$ of tobramycin were 10.7% and 6.6% lower, respectively, when tobramycin was coadministered with daptomycin. These differences were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of daptomycin is unknown.

Warfarin

In 16 healthy adult subjects, administration of daptomycin 6 mg/kg every 24h by IV infusion over a 30-minute period for 5 days, with coadministration of a single oral dose of warfarin (25 mg) on the 5th day, had no significant effect on the pharmacokinetics of either drug and did not significantly alter the INR (International Normalized Ratio).

Simvastatin

In 20 healthy adult subjects on a stable daily dose of simvastatin 40 mg, administration of daptomycin 4 mg/kg every 24h by IV infusion over a 30-minute period for 14 days (N=10) had no effect on plasma trough concentrations of simvastatin and was not associated with a higher incidence of adverse events, including skeletal myopathy, than in subjects receiving placebo once daily (N=10) *[see Warnings and Precautions (5.2) and Drug Interactions (7.1)]*.

Probenecid

Concomitant administration of probenecid (500 mg 4 times daily) and a single dose of daptomycin 4 mg/kg by IV infusion over a 30-minute period in adults did not significantly alter the C_{max} or $AUC_{0-\infty}$ of daptomycin.

12.4 Microbiology

Daptomycin belongs to the cyclic lipopeptide class of antibacterials. Daptomycin has clinical utility in the treatment of infections caused by aerobic, Gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin encompasses most clinically relevant Gram-positive pathogenic bacteria.

Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive bacteria *in vitro*. This has been demonstrated both by time-kill curves and by MBC/MIC (minimum bactericidal concentration/minimum inhibitory concentration) ratios using broth dilution methodology. Daptomycin maintained bactericidal activity *in vitro* against stationary phase *S. aureus* in simulated endocardial vegetations. The clinical significance of this is not known.

Mechanism of Action

Daptomycin binds to bacterial cell membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death.

Resistance

The mechanism(s) of daptomycin resistance is not fully understood. Currently, there are no known transferable elements that confer resistance to daptomycin.

Interactions with Other Antibacterials

In vitro studies have investigated daptomycin interactions with other antibacterials. Antagonism, as determined by kill curve studies, has not been observed. *In vitro* synergistic interactions of daptomycin with aminoglycosides, β-lactam antibacterials, and rifampin have been shown against some isolates of staphylococci (including some methicillin-resistant isolates) and enterococci (including some vancomycin-resistant isolates).

Complicated Skin and Skin Structure Infection (cSSSI) Trials in Adults

The emergence of daptomycin non-susceptible isolates occurred in 2 infected patients across the set of Phase 2 and pivotal Phase 3 clinical trials of cSSSI in adult patients. In one case, a non-susceptible *S. aureus* was isolated from a patient in a Phase 2 trial who received daptomycin at less than the protocol-specified dose for the initial 5 days of therapy. In the second case, a non-susceptible *Enterococcus faecalis* was isolated from a patient with an infected chronic decubitus ulcer who was enrolled in a salvage trial.

S. aureus Bacteremia/Endocarditis and Other Post-Approval Trials in Adults

In subsequent clinical trials in adult patients, non-susceptible isolates were recovered. *S. aureus* was isolated from a patient in a compassionate-use trial and from 7 patients in the *S. aureus* bacteremia/endocarditis trial *[see Clinical Studies (14.2)]*. An *E. faecium* was isolated from a patient in a vancomycin-resistant enterococci trial.

Antimicrobial Activity

Daptomycin has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Gram-Positive Bacteria

Enterococcus faecalis (vancomycin-susceptible isolates only)
Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus agalactiae
Streptococcus dysgalactiae subsp. *equisimilis*
Streptococcus pyogenes

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for daptomycin against isolates of similar genus or organism group.
However, the efficacy of daptomycin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

Corynebacterium jeikeium
Enterococcus faecalis (vancomycin-resistant isolates)
Enterococcus faecium (including vancomycin-resistant isolates)
Staphylococcus epidermidis (including methicillin-resistant isolates)
Staphylococcus haemolyticus

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for daptomycin, please see: https://www.fda.gov/STIC

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of daptomycin. However, neither mutagenic nor clastogenic potential was found in a battery of genotoxicity tests, including the Ames assay, a mammalian cell gene mutation assay, a test for chromosomal aberrations in Chinese hamster ovary cells, an *in vivo* micronucleus assay, an *in vitro* DNA repair assay, and an *in vivo* sister chromatid exchange assay in Chinese hamsters.

Daptomycin did not affect the fertility or reproductive performance of male and female rats when administered intravenously at doses of 25, 75, or 150 mg/kg/day, which is approximately up to 9 times the estimated human exposure level based upon AUCs (or approximately up to 4 times the recommended human dose of 6 mg/kg based on body surface area comparison).

13.2 Animal Toxicology and/or Pharmacology

Adult Animals

In animals, daptomycin administration has been associated with effects on skeletal muscle. However, there were no changes in cardiac or smooth muscle. Skeletal muscle effects were characterized by microscopic degenerative/regenerative changes and variable elevations in creatine phosphokinase (CPK). No fibrosis or rhabdomyolysis was evident in repeat-dose studies up to the highest doses tested in rats (150 mg/kg/day) and dogs (100 mg/kg/day). The degree of skeletal myopathy showed no increase when treatment was extended from 1 month to up to 6 months. Severity was dose-dependent. All muscle effects, including microscopic changes, were fully reversible within 30 days following the cessation of dosing.

In adult animals, effects on peripheral nerve (characterized by axonal degeneration and frequently accompanied by significant losses of patellar reflex, gag reflex, and pain perception) were observed at daptomycin doses higher than those associated with skeletal myopathy. Deficits in the dogs' patellar reflexes were seen within 2 weeks after the start of treatment at 40 mg/kg/day (9 times the human C_{max} at the 6 mg/kg/day dose), with some clinical improvement noted within 2 weeks after the cessation of dosing. However, at 75 mg/kg/day for 1 month, 7 of 8 dogs failed to regain full patellar reflex responses within a 3-month recovery period. In a separate study in dogs receiving doses of 75 and 100 mg/kg/day for 2 weeks, minimal residual histological changes were noted at 6 months after the cessation of dosing. However, recovery of peripheral nerve function was evident.

Tissue distribution studies in rats showed that daptomycin is retained in the kidney but appears to penetrate the blood-brain barrier only minimally following single and multiple doses.

Juvenile Animals

Target organs of daptomycin-related effects in 7-week-old juvenile dogs were skeletal muscle and nerve, the same target organs as in adult dogs. In juvenile dogs, nerve effects were noted at lower daptomycin blood concentrations than in adult dogs following 28 days of dosing. In contrast to adult dogs, juvenile dogs also showed evidence of effects in nerves of the spinal cord as well as peripheral nerves after 28 days of dosing. No nerve effects were noted in juvenile dogs following 14 days of dosing at doses up to 75 mg/kg/day.

Administration of daptomycin to 7-week-old juvenile dogs for 28 days at doses of 50 mg/kg/day produced minimal degenerative effects on the peripheral nerve and spinal cord in several animals, with no corresponding clinical signs. A dose of 150 mg/kg/day for 28 days produced minimal degeneration in the peripheral nerve and spinal cord as well as minimal to mild degeneration of the skeletal muscle in a majority of animals, accompanied by slight to severe muscle weakness evident in most dogs.
Following a 28-day recovery phase, microscopic examination revealed recovery of the skeletal muscle and the ulnar nerve effects, but nerve degeneration in the sciatic nerve and spinal cord was still observed in all 150 mg/kg/day dogs.

Following once-daily administration of daptomycin to juvenile dogs for 28 days, microscopic effects in nerve tissue were noted at a C_{max} value of 417 mcg/ml, which is approximately 3-fold less than the C_{max} value associated with nerve effects in adult dogs treated once daily with daptomycin for 28 days (1308 mcg/ml).

Neonatal Animals

Neonatal dogs (4 to 31 days old) were more sensitive to daptomycin-related adverse nervous system and/or muscular system effects than either juvenile or adult dogs. In neonatal dogs, adverse nervous system and/or muscular system effects were associated with a C_{max} value approximately 3-fold less than the C_{max} in juvenile dogs, and 9-fold less than the C_{max} in adult dogs following 28 days of dosing.
At a dose of 25 mg/kg/day with associated C_{max} and AUC_{inf} values of 147 mcg/ml and 717 mcg•h/ml, respectively (1.6 and 1.0-fold the adult human C_{max} and AUC, respectively, at the 6 mg/kg/day dose), mild clinical signs of twitching and one incidence of muscle rigidity were observed with no corresponding effect on body weight. These effects were found to be reversible within 28 days after treatment had stopped.

At higher dose levels of 50 and 75 mg/kg/day with associated C_{max} and AUC_{inf} values of ≥321 mcg/ml and ≥1470 mcg•h/ml, respectively, marked clinical signs of twitching, muscle rigidity in the limbs, and impaired use of limbs were observed. Resulting decreases in body weights and overall body condition at doses ≥50 mg/kg/day necessitated early discontinuation by postnatal day (PND) 19.

Histopathological assessment did not reveal any daptomycin-related changes in the peripheral and central nervous system tissue, as well as in the skeletal muscle or other tissues assessed, at any dose level.

No adverse effects were observed in the dogs that received daptomycin at 10 mg/kg/day, the NOAEL, with associated C_{max} and AUC_{inf} values of 62 mcg/ml and 247 mcg•h/ml, respectively (or 0.6 and 0.4- fold the adult human C_{max} and AUC, respectively at the 6 mg/kg dose).

14 CLINICAL STUDIES

14.1 Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections (cSSSI) (Table 9) were enrolled in two randomized, multinational, multicenter, investigator-blinded trials comparing daptomycin (4 mg/kg IV every 24h) with either vancomycin (1 g IV q12h) or an anti-staphylococcal semi- synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g IV per day). Patients could switch to oral therapy after a minimum of 4 days of IV treatment if clinical improvement was demonstrated. Patients known to have bacteremia at baseline were excluded. Patients with creatinine clearance (CL_{CR}) between 30 and 70 ml/min were to receive a lower dose of daptomycin as specified in the protocol; however, the majority of patients in this subpopulation did not have the dose of daptomycin adjusted.

Table 9: Investigator's Primary Diagnosis in the cSSSI Trials in Adult Patients (Population: ITT)

Primary Diagnosis	Adult Patients (Daptomycin/ Comparator*)		
	Study 9801 N=264 / N=266	Study 9901 N=270 / N=292	Pooled N=534 / N=558
Wound Infection	99 (38%) / 116 (44%)	102 (38%) / 108 (37%)	201 (38%) / 224 (40%)
Major Abscess	55 (21%) / 43 (16%)	59 (22%) / 65 (22%)	114 (21%) / 108 (19%)
Ulcer Infection	71 (27%) / 75 (28%)	53 (20%) / 68 (23%)	124 (23%) / 143 (26%)
Other Infection†	39 (15%) / 32 (12%)	56 (21%) / 51 (18%)	95 (18%) / 83 (15%)

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).
† The majority of cases were subsequently categorized as complicated cellulitis, major abscesses, or traumatic wound infections.

One trial was conducted primarily in the United States and South Africa (study 9801), and the second was conducted at non-US sites only (study 9901). The two trials were similar in design but differed in patient characteristics, including history of diabetes and peripheral vascular disease. There were a total of 534 adult patients treated with daptomycin and 558 treated with comparator in the two trials. The majority (89.7%) of patients received IV medication exclusively.

The efficacy endpoints in both trials were the clinical success rates in the intent-to-treat (ITT) population and in the clinically evaluable (CE) population. In study 9801, clinical success rates in the ITT population were 62.5% (165/264) in patients treated with daptomycin and 60.9% (162/266) in patients treated with comparator drugs. Clinical success rates in the CE population were 76.0% (158/208) in patients treated with daptomycin and 76.7% (158/206) in patients treated with comparator drugs. In study 9901, clinical success rates in the ITT population were 80.4% (217/270) in patients treated with daptomycin and 80.5% (235/292) in patients treated with comparator drugs. Clinical success rates in the CE population were 89.9% (214/238) in patients treated with daptomycin and 90.4% (226/250) in patients treated with comparator drugs.

The success rates by pathogen for microbiologically evaluable patients are presented in Table 10.

Table 10: Clinical Success Rates by Infecting Pathogen in the cSSSI Trials in Adult Patients (Population: Microbiologically Evaluable)

Pathogen	Success Rate n/N (%)	
	Daptomycin	Comparator*
Methicillin-susceptible *Staphylococcus aureus* (MSSA)†	170/198 (86%)	180/207 (87%)
Methicillin-resistant *Staphylococcus aureus* (MRSA)†	21/28 (75%)	25/36 (69%)
Streptococcus pyogenes	79/84 (94%)	80/88 (91%)
Streptococcus agalactiae	23/27 (85%)	22/29 (76%)
Streptococcus dysgalactiae subsp. *equisimilis*	8/8 (100%)	9/11 (82%)
Enterococcus faecalis (vancomycin-susceptible only)	27/37 (73%)	40/53 (76%)

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).
† As determined by the central laboratory.

14.2 *S. aureus* Bacteremia/Endocarditis

Adults with *S. aureus* Bacteremia/Endocarditis

The efficacy of daptomycin in the treatment of adult patients with *S. aureus* bacteremia was demonstrated in a randomized, controlled, multinational, multicenter, open-label trial. In this trial, adult patients with at least one positive blood culture for *S. aureus* obtained within 2 calendar days prior to the first dose of study drug and irrespective of source were enrolled and randomized to either daptomycin (6 mg/kg IV every 24h) or standard of care [an anti-staphylococcal semi-synthetic penicillin 2 g IV q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g IV q12h, each with initial gentamicin 1 mg/kg IV every 8 hours for first 4 days]. Of the patients in the comparator group, 93% received initial gentamicin for a median of 4 days, compared with 1 patient (<1%) in the daptomycin group. Patients with prosthetic heart valves, intravascular foreign material that was not planned for removal within 4 days after the first dose of study medication, severe neutropenia, known osteomyelitis, polymicrobial bloodstream infections, creatinine clearance <30 ml/min, and pneumonia were excluded.

Upon entry, patients were classified for likelihood of endocarditis using the modified Duke criteria (Possible, Definite, or Not Endocarditis). Echocardiography, including a transesophageal echocardiogram (TEE), was performed within 5 days following study enrollment. The choice of comparator agent was based on the oxacillin susceptibility of the *S. aureus* isolate. The duration of study treatment was based on the investigator's clinical diagnosis. Final diagnoses and outcome assessments at Test of Cure (6 weeks after the last treatment dose) were made by a treatment-blinded Adjudication Committee, using protocol-specified clinical definitions and a composite primary efficacy endpoint (clinical and microbiological success) at the Test of Cure visit.

A total of 246 patients ≥18 years of age (124 daptomycin, 122 comparator) with *S. aureus* bacteremia were randomized from 48 centers in the US and Europe. In the ITT population, 120 patients received daptomycin and 115 received comparator (62 received an anti-staphylococcal semi-synthetic penicillin and 53 received vancomycin). Thirty-five patients treated with an anti-staphylococcal semi-synthetic penicillin received vancomycin initially for 1 to 3 days, pending final susceptibility results for the *S. aureus* isolates. The median age among the 235 patients in the ITT population was 53 years (range: 21 to 91 years); 30/120 (25%) in the daptomycin group and 37/115 (32%) in the comparator group were ≥65 years of age. Of the 235 ITT patients, there were 141 (60%) males and 156 (66%) Caucasians across the two treatment groups. In addition, 176 (75%) of the ITT population had systemic inflammatory response syndrome (SIRS) at baseline and 85 (36%) had surgical procedures within 30 days prior to onset of the *S. aureus* bacteremia. Eighty-nine patients (38%) had bacteremia caused by methicillin- resistant *S. aureus* (MRSA). Entry diagnosis was based on the modified Duke criteria and comprised 37 (16%) Definite, 144 (61%) Possible, and 54 (23%) Not Endocarditis. Of the 37 patients with an entry diagnosis of Definite Endocarditis, all (100%) had a final diagnosis of infective endocarditis, and of the 144 patients with an entry diagnosis of Possible Endocarditis, 15 (10%) had a final diagnosis of infective endocarditis as assessed by the Adjudication Committee. Of the 54 patients with an entry diagnosis of Not Endocarditis, 1 (2%) had a final diagnosis of infective endocarditis as assessed by the Adjudication Committee.

In the ITT population, there were 182 patients with bacteremia and 53 patients with infective endocarditis as assessed by the Adjudication Committee, including 35 with right-sided endocarditis and 18 with left-sided endocarditis. The 182 patients with bacteremia comprised 121 with complicated *S. aureus* bacteremia and 61 with uncomplicated *S. aureus* bacteremia.

Complicated bacteremia was defined as *S. aureus* isolated from blood cultures obtained on at least 2 different calendar days, and/or metastatic foci of infection (deep tissue involvement), and classification of the patient as not having endocarditis according to the modified Duke criteria. Uncomplicated bacteremia was defined as *S. aureus* isolated from blood culture(s) obtained on a single calendar day, no metastatic foci of infection, no infection of prosthetic material, and classification of the patient as not having endocarditis according to the modified Duke criteria. The definition of right-sided infective endocarditis (RIE) used in the clinical trial was Definite or Possible Endocarditis according to the modified Duke criteria and no echocardiographic evidence of predisposing pathology or active involvement of either the mitral or aortic valve. Complicated RIE comprised patients who were not intravenous drug users, had a positive blood culture for MRSA, serum creatinine ≥2.5 mg/dL, or evidence of extrapulmonary sites of infection. Patients who were intravenous drug users, had a positive blood culture for methicillin-susceptible *S. aureus* (MSSA), had serum creatinine <2.5 mg/dL, and were without evidence of extrapulmonary sites of infection were considered to have uncomplicated RIE.

The coprimary efficacy endpoints in the trial were the Adjudication Committee success rates at the Test of Cure visit (6 weeks after the last treatment dose) in the ITT and Per Protocol (PP) populations. The overall Adjudication Committee success rates in the ITT population were 44.2% (53/120) in patients treated with daptomycin and 41.7% (48/115) in patients treated with comparator (difference = 2.4% [95% CI −10.2, 15.1]). The success rates in the PP population were 54.4% (43/79) in patients treated with daptomycin and 53.3% (32/60) in patients treated with comparator (difference = 1.1% [95% CI −15.6, 17.8]).

Adjudication Committee success rates are shown in Table 11.

Table 11: Adjudication Committee Success Rates at Test of Cure in the *S. aureus* Bacteremia/Endocarditis Trial in Adult Patients (Population: ITT)

Population	Success Rate n/N (%)		Difference: Daptomycin− Comparator (Confidence Interval)
	Daptomycin 6 mg/kg	Comparator*	
Overall	53/120 (44%)	48/115 (42%)	2.4% (−10.2, 15.1)†
Baseline Pathogen			
Methicillin-susceptible *S. aureus*	33/74 (45%)	34/70 (49%)	−4.0% (−22.6, 14.6)‡
Methicillin-resistant *S. aureus*	20/45 (44%)	14/44 (32%)	12.6% (−10.2, 35.5)‡
Entry Diagnosis§			
Definite or Possible Infective Endocarditis	41/90 (46%)	37/91 (41%)	4.9% (−11.6, 21.4)‡
Not Infective Endocarditis	12/30 (40%)	11/24 (46%)	−5.8% (−36.2, 24.5)‡
Final Diagnosis			
Uncomplicated Bacteremia	18/32 (56%)	16/29 (55%)	1.1% (−31.7, 33.9)¶
Complicated Bacteremia	26/60 (43%)	23/61 (38%)	5.6% (−17.3, 28.6)¶
Right-Sided Infective Endocarditis	8/19 (42%)	7/16 (44%)	−1.6% (−44.9, 41.6)¶
Uncomplicated Right- Sided Infective Endocarditis	3/6 (50%)	1/4 (25%)	25.0% (−51.6, 100.0)¶
Complicated Right-Sided Infective Endocarditis	5/13 (39%)	6/12 (50%)	−11.5% (−62.4, 39.4)¶
Left-Sided Infective Endocarditis	1/9 (11%)	2/9 (22%)	−11.1% (−55.9, 33.6)¶

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.
† 95% Confidence Interval
‡ 97.5% Confidence Interval (adjusted for multiplicity)
§ According to the modified Duke criteria[5]
¶ 99% Confidence Interval (adjusted for multiplicity)

Eighteen (18/120) patients in the daptomycin arm and 19/116 patients in the comparator arm died during the trial. These comprise 3/28 daptomycin-treated patients and 8/26 comparator-treated patients with endocarditis, as well as 15/92 daptomycin-treated patients and 11/90 comparator-treated patients with bacteremia. Among patients with persisting or relapsing *S. aureus* infections, 8/19 daptomycin-treated patients and 7/11 comparator-treated patients died.

Overall, there was no difference in time to clearance of *S. aureus* bacteremia between daptomycin and comparator. The median time to clearance in patients with MSSA was 4 days and in patients with MRSA was 8 days.

Failure of treatment due to persisting or relapsing *S. aureus* infections was assessed by the Adjudication Committee in 19/120 (16%) daptomycin-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (10%) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with an anti-staphylococcal semi-synthetic penicillin). Among all failures, isolates from 6 daptomycin-treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility) by central laboratory testing during or following therapy. Most patients who failed due to persisting or relapsing *S. aureus* infection had deep-seated infection and did not receive necessary surgical intervention *[see Warnings and Precautions (5.9)]*.

15 REFERENCES

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4. Klibanov OM, Vickery S, Nortey C: Successful treatment of infective panniculitis with daptomycin in a pregnant, morbidly obese patient. Ann Pharmacother 48(5):652-655, 2014.
5. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–638.

16 HOW SUPPLIED/STORAGE AND HANDLING

DAPTOMYCIN – TRIMA 500 mg (daptomycin for injection/infusion) is supplied as a sterile pale yellow to light brown lyophilized cake or powder in a single use 15 ml type I glass vial with 20 mm bromobutyl grey rubber stoppers and 20 mm, blue flip-off seal containing 500 mg of daptomycin: Package of 1.

Store original packages at refrigerated temperatures, 2°C to 8°C. Storage conditions for the reconstituted and diluted solutions are described in another section of the prescribing information [see Dosage and Administration (2.5)].

The expiry date of the product is indicated on the packaging materials.

License Holder and Importer: Trima Israel Pharmaceutical Products Maabarot Ltd. Kibbutz Maabarot 4023000.

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