RISK MANAGEMENT PLAN:

EU QPPV AND CONTACT PERSON FOR THIS RMP

Active substance(s): Daptomycin

Product(s) concerned: Cubicin

MAH / MAA name: Merck Sharp & Dohme B.V.

EU Qualified Person for Pharmacovigilance (QPPV) name:	Guy Demol
EU QPPV signature:	[redacted]
Date of signature:	

Contact person for this RMP:	[redacted]
Contact person e-mail address:	
Contact person telephone number:	

[redacted]

EU RISK MANAGEMENT PLAN (RMP) FOR

Daptomycin

RMP version to be assessed as part of this application:

RMP Version number: 12.0

Data lock point for this RMP: 11-SEP-2018

Date of final sign off: 14-FEB-2020

Rationale for submitting an updated RMP: Revision of risks in alignment with EMA Guideline on Good Pharmacovigilance Practices (GVP) Module V (Revision 2) and retirement of Additional Risk Minimization Measures (ARMM) based on the assessment of clinical, nonclinical, and postmarketing data available to 11-SEP-2018.

Summary of significant changes in this RMP: The significant changes in this RMP include updates to the RMP template, and re-evaluation of safety concerns based on GVP Module V (Revision 2). In accordance with this guidance, all *Important Identified Risks*, *Important Potential Risks* and *Missing Information* have been removed from the list of safety concerns in this version of the RMP. The MAH has also retired the educational material considered ARMM: "Cubicin® – A Guide to Dosing" and "Antibiotic Susceptibility Testing with Cubicin® (daptomycin)."

Other RMP versions under evaluation: not applicable

Details of the currently approved RMP:

Version number: 10.2
Approved with procedure: EMEA/H/C/0637/IAIN/0068
Date of approval (opinion date): 12-FEB-2018

QPPV name: Guy Demol, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF TABLES

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LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzymes
ADR	Adverse drug reaction
AE	Adverse experience
AGEP	Acute generalized exanthematous pustulosis
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
AUC	Area Under the Curve
BID	Twice a day
CAPD	Continuous ambulatory peritoneal dialysis
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
cSSSI	Complicated skin/skin structure infections or complicated skin/soft tissue infections (used interchangeably with cSSTI throughout this document, as these are clinically equivalent indications)
cSSTI	Complicated skin/soft tissue infections (used interchangeably with cSSSI throughout this document)
CHD	Coronary heart disease
Cmax	Maximum concentration
Cmin	Minimum (trough) concentration
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CT	Computed tomography
CVD	Cardiovascular disease
DLP	Data lock point
DNA	Deoxyribonucleic acid
DPN	Diabetic polyneuropathy
ECG / EKG	Electrocardiogram
ESRD	End stage renal disease
GPRD	General Practice Research Database
HCP	Healthcare professional
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HLT	High Level Term
HMG CoA	3-Hydroxy-3-methyl glutaryl coenzyme A
HPN	Hereditary polyneuropathy
HSR	Hypersensitivity reaction
HSS	Hypersensitivity syndrome

[redacted]

IBD	International Birth Date
ICU	Intensive care unit
IDPN	Idiopathic polyneuropathy
IDU	Intravenous drug users
IE	Infective endocarditis
IM	Intramuscular(ly)
INN	International Nonproprietary Name
INR	International normalized ratio
IV	Intravenous(ly)
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
M/E	Myeloid/erythroid
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
N/A	Not applicable
NOEL	No Observed Effects Level
PAES	Post-authorization efficacy study
PND	Postnatal days
PO	Oral(ly)
PSUR	Periodic Safety Update Report
PT	Preferred Term
RIE	Right-sided infective endocarditis
RMP	Risk Management Plan
SA	*Staphylococcus aureus*
SAB	*Staphylococcus aureus* bacteremia
SAE	Serious adverse event
SMQ	Standard MedDRA Query
SOC	System Organ Class
UK	United Kingdom
USA	United States of America
WBC	White blood cell count

[redacted]

PART I: PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	Daptomycin
Pharmacotherapeutic group(s) (ATC Code)	J01XX09
Marketing Authorisation Holder	Merck Sharp & Dohme B.V.
Number of medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Cubicin
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Daptomycin is a cyclic lipopeptide natural product that is active against Gram-positive bacteria only. Summary of mode of action: Daptomycin acts by binding (in the presence of calcium ions) to bacterial membranes of both growing and stationary phase cells causing depolarisation and leading to a rapid inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.
Hyperlink to the Prescribing Information	Refer to the approved Summary of Product Characteristics updated in EMEA/H/C/000637/IA/0071/G approved on 14-DEC-2018
Indication(s) in the EEA:	Cubicin is indicated for the treatment of the following infections: -Adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI) -Adult patients with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. - Adult and paediatric (1 to 17 years of age) patients with *Staphylococcus aureus* bacteraemia (SAB). In adults, use in bacteraemia should be associated with RIE or with cSSTI, while in paediatric patients, use in bacteraemia should be associated with cSSTI. Daptomycin is active against Gram positive bacteria only. In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s). Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Dosage in the EEA:	Adults: -cSSTI without concurrent *Staphylococcus aureus* bacteremia (SAB): Cubicin 4 mg/kg is administered once every 24 hours for 7-14 days or until the infection is resolved -cSSTI with concurrent SAB: Cubicin 6 mg/kg is administered once every 24 hours; duration of therapy may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient

[redacted]

Table Part I.1: Product Overview

<table>
<tr><td></td><td>
-Known or suspected right-sided infective endocarditis due to Staphylococcus aureus: Cubicin 6 mg/kg is administered once every 24 hours; duration of therapy should be in accordance with available official recommendations

-See SmPC for dose adjustments in patients with renal impairment

<u>Paediatric patients (1 to 17 years of age):</u>

The recommended dosage regimens for paediatric patients based on age and indication are shown below.
<table>
<tr><th rowspan="2">Age Group</th><th colspan="4">Indication</th></tr>
<tr><th colspan="2">cSSTI without SAB</th><th colspan="2">cSSTI associated with SAB</th></tr>
<tr><th>Dosage Regimen</th><th>Duration of Therapy</th><th>Dosage Regimen</th><th>Duration of Therapy</th></tr>
<tr><td>12 to 17 years</td><td>5 mg/kg once every 24 hours infused over 30 minutes</td><td rowspan="4">Up to 14 days</td><td>7 mg/kg once every 24 hours infused over 30 minutes</td><td rowspan="4">(1)</td></tr>
<tr><td>7 to 11 years</td><td>7 mg/kg once every 24 hours infused over 30 minutes</td><td>9 mg/kg once every 24 hours infused over 30 minutes</td></tr>
<tr><td>2 to 6 years</td><td>9 mg/kg once every 24 hours infused over 60 minutes</td><td>12 mg/kg once every 24 hours infused over 60 minutes</td></tr>
<tr><td>1 to <2 years</td><td>10 mg/kg once every 24 hours infused over 60 minutes</td><td>12 mg/kg once every 24 hours infused over 60 minutes</td></tr>
<tr><td colspan="5">cSSTI = complicated skin and soft-tissue infections; SAB = S. aureus bacteraemia

(1) Minimum duration of Cubicin for paediatric SAB should be in accordance with the perceived risk of complications in the individual patient. The duration of Cubicin may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient. In the paediatric SAB study, the mean duration of IV Cubicin was 12 days, with a range of 1 to 44 days. The duration of therapy should be in accordance with available official recommendations.</td></tr>
</table>
Pediatric patients below the age of one year should not be given Cubicin due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs (see SmPC section 5.3; see also Part II: Module SII below).

Please refer to the current SmPC for additional dosing information.
</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>350 mg and 500 mg, powder for solution for injection or infusion

A pale yellow to light brown lyophilised cake or powder</td></tr>
<tr><td>Is/will the product be subject to additional monitoring?</td><td>No</td></tr>
</table>

[redacted]

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Complicated Skin and Soft Tissue Infections (cSSTI), and *S. aureus* bacteremia associated with cSSTI

Incidence:

Gram-positive bacteria are a major cause of serious infections such as cSSTI, bacteremia and infective endocarditis (IE). *Staphylococcus aureus* bacteremia (SAB) is often a consequence of cSSTI, and IE is an additional possible associated complication of SAB [Ref. 5.4: 0496LC], [Ref. 5.4: 0496JC]. *Staphylococcus aureus* (SA) and Beta-hemolytic Streptococci (BHS) are some of the most prevalent pathogens [Ref. 5.4: 0496K8], [Ref. 5.4: 04GZXZ], [Ref. 5.4: 04H2L3], [Ref. 5.4: 04H0Q3] associated with cSSTI. *S. aureus* strains are typically categorized as being methicillin-susceptible *S. aureus* or methicillin-resistant *S. aureus* (MRSA). Over the last few decades, MRSA has emerged as a clinically significant cause of community-acquired and nosocomial *S. aureus* infections, including cSSTI and SAB (Liu, et al., IDSA Guidelines, 2011) [Ref. 5.4: 04WP6N]. MRSA has been identified as a serious public health threat by the Centers for Disease Control and Prevention (CDC) and is considered a pathogen of high priority with a need for new antibiotics by the World Health Organization (WHO 2017, [Ref. 5.4: 04W8X9], CDC 2013 [Ref. 5.4: 04PX8F]).

While cSSTI represents a significant clinical problem, the overall global incidence of cSSTI is not well described. [Ref. 5.4: 050H9M] However, skin and skin structure infections are very common, frequently encountered in both community and hospital settings, and are common causes of presentation to emergency departments. One study conducted in the US reported incidence rates of clinically diagnosed SSTI ranging from 440 to 652 per 10,000 patients-year depending on age groups. [Ref. 5.4: 04H0JY]

A single center study conducted in Spain found that the cumulative incidence of MRSA bloodstream infections was reported to be 10 episodes per 100,000 person days over a 19-year study period. [Ref. 5.4: 04H2LM] In addition, a study conducted in the US reported an overall incidence of invasive MRSA infection (regardless of whether the infection was acquired in the community or at a health care facility) ranging between 19.3 and 40.4 infections per 100,000 population depending on the geographical area and patient characteristics. [Ref. 5.4: 03PVSD] In addition, a recent review found that MRSA infections are estimated to affect 150,000 patients per year in the EU. [Ref. 5.4: 04BWFW]

Prevalence:

The global prevalence of cSSTI is not known. In a study utilizing claims data from a Taiwan national health insurance program, the point prevalence of SSTI of the sampled population. (N=146,686) was 7.7%. [Ref. 5.4: 04H0K5] In addition, Jones et al 2003 [Ref. 5.4: 03PR8H] reported that SSTI accounted for approximately 10% of hospital admissions to an infectious

[redacted]

disease unit. In 1995, an estimated number of 330,000 patients in the USA and about 4,300 patients in Scotland required hospital treatment for SSTI, representing about 0.1% of the adult population. [Ref. 5.4: 0496K8]

In a recent review of SSTIs, SA was reported to account for 44.6% of all isolates in North America. [Ref. 5.4: 04H0JW] In addition, a review of the burden of MRSA in Europe estimated MRSA to account for more than 40% of all reported HAIs. [Ref. 5.4: 04BWFW] A large multicenter study found that MRSA prevalence varied considerably by geographic region ranging from 22.8% in Europe to 44.4% in the US.

Demographics of the population in the authorised indication: and risk factors for the disease:

Skin infections can occur in any age group or sex. However, elderly patients are at higher risk. [Ref. 5.4: 04H0QP], [Ref. 5.4: 04H0QB] In addition, the risk increases in patients with underlying diseases, such as Human Immunodeficiency Virus (HIV) infection, and differences in immune response or differences in socioeconomic factors (e.g., decreased access to medical care). [Ref. 5.4: 04H0QB]

Patients with comorbid conditions such as diabetes mellitus or ischemic ulceration are at particularly high risk for cSSTI. [Ref. 5.4: 04H0JY] Recent history of physical trauma has also been identified as a risk factor for cSSTI in children. [Ref. 5.4: 04CXQY]

The main existing treatment options:

The treatment of cSSTI caused by resistant bacteria relies on a combination of surgical and antimicrobial treatment. The efficacy and tolerability of linezolid, tedizolid, telavancin, dalbavancin, tigecycline, ceftaroline, daptomycin, and vancomycin for treatment of cSSTI due to MRSA in adults have been demonstrated [Ref. 5.4: 04H33S]. Currently approved treatment options in pediatric patients with cSSTI caused by MRSA include daptomycin, clindamycin, vancomycin and linezolid. [Ref. 5.4: 04FQ7S]; [Ref. 5.4: 04Y980]; [Ref. 5.4: 043M72]

These drugs are associated with comparable clinical cure and eradication rates. Of these drugs, linezolid has been administered to the largest number of patients in clinical trials with active comparator, typically against vancomycin. Tigecycline is an alternative therapeutic agent for polymicrobial infections excluding diabetic foot infections. Daptomycin is an effective treatment option for cases of cSSTI and SA (including MRSA) bacteremia. Due to its pharmacokinetic requirement for therapeutic drug monitoring, risk for nephrotoxicity, and the increasing resistance and poor clinical results in the treatment of severe infections, the administration of vancomycin should be restricted only to cases of mild or moderate severity of infection or if other treatment options are not tolerated or available. [Ref. 5.4: 04GZ2Z]

[redacted]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

No specific data for the overall mortality of cSSTI with gram positive bacteria were found in the published literature. A study utilizing claims data from a Taiwan national health insurance program found all-cause mortality rate of 2.7% among patients with SSTIs [Ref. 5.4: 04H0K5] Mortality rates associated with complicated SA infections have been reported to be as high as 20-25%. [Ref. 5.4: 03PVSD]

Children with cSSTI are at risk of developing bacteremic staphylococcal infection, which may be fatal. [Ref. 5.4: 04DW24] In a case-series of 16 children (median age 6.5 years) with invasive gram-positive bacterial infections (15 with Staphylococcal disease), 2 patients (12.5%) died during hospitalization. [Ref. 5.4: 04CXQY]

Important co-morbidities:

- Diabetes mellitus
- Cardiovascular disease
- Renal impairment

Right-sided Infective Endocarditis (RIE) due to *S. aureus* in adults

Incidence:

The incidence of RIE due to SA in the general population is not known. The overall incidence of IE among intravenous drug users (IDU), the main risk group for RIE, is estimated to be 1.5-2.0 per 1,000 patients per year. [Ref. 5.4: 04GX9D], [Ref. 5.4: 04H0QN] The most commonly isolated pathogen is SA, which accounts for up to 70% of IE infections in this population. [Ref. 5.4: 0496JN] A recent analysis of three French population-based surveys sent to physicians involved in IE patient care, echocardiographers, and microbiologists, found that the incidence of IE and SA IE was 32 (95%CI: 28 to 35) cases per million and 8.2 (95%CI: 6.6 to 10.2) cases per million respectively. [Ref. 5.4: 04GZY4]

A recent study including 16 countries from Europe/Middle East, Australia/New Zealand, Brazil, and the USA, reported that SA was identified in 31.4% of all definite IE cases (n=1779). [Ref. 5.4: 0496LC] Among IDUs from an inner city demographic area presenting with fever, 13% showed echocardiographic evidence of IE. In addition, among IDUs with bacteremia, up to 41% have echocardiographic evidence of IE. [Ref. 5.4: 0496JN]

A recent review reported incidence rates of RIE ranging from 2-4 cases per 1,000 years of IDU. However, these rates were from studies published in the 1990s. Recent estimates were not found in the published literature.

[redacted]

Prevalence:

No specific data for prevalence of RIE due to SA in the general population were found in the published literature. Since RIE is an acute illness, the prevalence is anticipated to be low even among IDU and other risk groups.

Demographics of the population in the authorised indication: and risk factors for the disease:

RIE due to SA largely affects IDUs, a patient population mainly consisting of young males. HIV-positive patients also have a higher risk for right-side involvement. [Ref. 5.4: 0496JN] In addition, older age, presence of comorbid diseases such as diabetes or congenital heart disease, and presence of implanted medical devices (e.g. prosthetic heart valves, catheters, etc.) are risk factors for the development of RIE.[Ref. 5.4: 04H0K3]

The main existing treatment options:

Endocarditis caused by *Staphylococcus aureus* in the absence of prosthetic valves: Endocarditis in IDUs – In this patient population, no standard therapies exist for the treatment of IE caused by SA [Ref. 5.4: 04Y7TP]; [Ref. 5.4: 043M72]. In IDUs with uncomplicated SA RIE, several therapy regimens have been described: combined beta-lactam aminoglycoside, cloxacillin monotherapy, cloxacillin plus gentamicin, glycopeptide (teicoplanin or vancomycin) plus gentamicin, beta-lactam short-course therapy, with or without aminoglycoside. Endocarditis in Non-IDUs - Use of gentamicin-nafcillin therapy may be of benefit in patients who fail to respond to monotherapy with nafcillin. Vancomycin therapy is recommended for SA endocarditis in patients with anaphylactoid beta-lactam allergies; however, therapy outcomes might be suboptimal with vancomycin therapy for serious SA infections. Vancomycin therapy is recommended for MRSA endocarditis. Rifampin monotherapy or rifampin in combination with nafcillin, oxacillin, vancomycin, trimethoprim/sulfamethoxazole, or aminoglycosides may be used. However, efficacy is highly variable [Ref. 5.4: 04Y7TP]

Endocarditis in the presence of prosthetic valves or other prosthetic material caused by SA: Because of the high mortality rate associated with SA prosthetic valve endocarditis, combination antimicrobial therapy is recommended. For RIE due to *Staphylococcus aureus* infection caused by an oxacillin-susceptible strain, nafcillin or oxacillin together with rifampin is suggested; with oxacillin- resistant Staphylococci, vancomycin and rifampin should be used. If the strains are resistant to gentamicin, then a fluoroquinolone may be used if the strain is susceptible. In summary, a 2-week regimen of aminoglycoside is recommended for Staphylococcal prosthetic valve endocarditis because of the associated high morbidity and mortality rates for such infections. Recommendation is based on limited clinical data [Ref. 5.4: 04H0DC].

Natural history of the indicated condition including mortality and morbidity:

SA endocarditis is invariably fatal if untreated. Mortality associated with antimicrobial treatment for SA RIE is not well described. A recent study of patients with RIE requiring

[redacted]

ICU admission in 10 hospitals in France reported a mortality rate of 21.6%. [Ref. 5.4: 04YD6G] In-hospital mortality due to *Staphylococcus aureus*, among all IE patients, varied from 37.1% in 1991 to 35.2% in 2008. [Ref. 5.4: 04GZY4] The 90-day mortality associated with SA IE was lower in IDU (10%) compared to non-IDU patients (39%). [Ref. 5.4: 04H0K3] Overall mortality rates for IE range from 15% to 40% depending on time period, study, clinical factors, and geographic region. [Ref. 5.4: 0496LC] [Ref. 5.4: 04GZY4] [Ref. 5.4: 050H9N]

Although mortality of RIE is lower compared to left-sided IE [Ref. 5.4: 04GX9D], local consequences such as cardiac complications (i.e. conduction system abnormalities, severe valvular regurgitation causing right-sided heart failure) may develop. Systemic consequences include septic pulmonic emboli, pleural effusion, empyema, neurologic, renal and other complications which can cause significant morbidity. [Ref. 5.4: 0496JN] Infections caused by MRSA are associated with longer hospital stays, longer duration of antibiotic use, and greater mortality rates compared to MSSA. [Ref. 5.4: 048Q52]

Important co-morbidities:

- Diabetes mellitus
- Cardiovascular disease
- Renal impairment

***Staphylococcus aureus* Bacteremia (SAB) When Associated with RIE or with cSSTI**

Incidence:

No specific data for incidence of bacteremia due to SA when associated with RIE or cSSTI were found in the published literature. However, the incidence of SA IE was estimated to be 5.2, 6.8 and 8.2 per million in 1991, 1999 and 2008 respectively in 3 different population based surveys in France. [Ref. 5.4: 04GZY4] In a prospective multicenter observational study in Czech Republic, crude incidence of IE was 3.4 cases per 100,000 inhabitants with SA isolated in 29.9% of cases. [Ref. 5.4: 04H0QT] In a retrospective cohort study in the US (1999-2008), admissions associated with *Staphylococcus* rose from 3.3 to 5.4 cases per 100,000 population years during the study period. [Ref. 5.4: 04GZ4K]

A recent summary of population-based studies reported incidence rates of SAB ranging from 11 to 30 per 100,000 populations, with rates varying by geographic location and study. [Ref. 5.4: 04H0QD] In a study that involved patients with prosthetic cardiac valves, the incidence of IE among patients with SAB was 43% (the incidence was 33% at the time when bacteremia was discovered and 11% at a mean of 45 days after diagnosis) [Ref. 5.4: 04H0QX]. In a study that involved 430 adults with SAB, RIE occurred significantly more frequently among injection drug users compared to non-IDU's (46% vs. 14%). [Ref. 5.4: 04H0K3]

Prevalence:

No specific data for prevalence of bacteremia due to SA when associated with RIE or cSSTI were found in the published literature. In a Danish study among 244 SAB patients, 22% were diagnosed with IE. [Ref. 5.4: 04H3XT] In general, SA, particularly MRSA, has become one of the most common pathogens isolated in hospital-acquired bacteremia. [Ref. 5.4: 04GZ48] The UK, Ireland and Greece had some of the highest rates of MRSA blood culture isolates with a prevalence of over 40% among the SA strains. [Ref. 5.4: 04F8J8]

Demographics of the population in the authorised indication: and risk factors for the disease:

Several factors associated with an increased risk of developing SAB have been identified, including previous MRSA infection or colonization, skin ulcers or cellulitis at hospital admission, presence of central venous catheters [Ref. 5.4: 04H2L2], urinary catheter insertion, surgical site infection [Ref. 5.4: 04GZTR], IDU, presence of immunosuppressive conditions, use of corticosteroids, and liver disease. [Ref. 5.4: 04H0QL] SA IE occurs frequently among IDU (typically RIE) and in patients with prosthetic heart valves and intravascular devices. [Ref. 5.4: 04H2LK], [Ref. 5.4: 04H0K3] In addition, the following patient groups are at increased risk of SA IE: persons receiving renal hemodialysis or have received vancomycin treatment and patients with type I diabetes mellitus or with intravascular devices, MRSA infection, or persistent bacteremia. [Ref. 5.4: 0496LC]

The main existing treatment options:

Vancomycin and daptomycin are first-line antibiotic therapies for MRSA bacteremia. It has also been suggested that linezolid might be effective for treating gram-positive bacteremia. Several other antibiotics have either preliminary or limited data on the treatment of MRSA bacteremia. Data from a single randomized trial suggested that dalbavancin is a potential alternative to vancomycin for catheter- related, gram-positive bacteremia. Data from an emergency-use program suggested that quinupristin-dalfopristin maybe a therapeutic option for MRSA infections, including bacteremia. However, this antibiotic combination is associated with an unfavorable adverse event profile, including infusion site pain, nausea, and myalgia. Telavancin is a lipoglycopeptide antibiotic approved for complicated cSSTI and hospital-acquired and ventilator-associated bacterial pneumonia caused by SA. Combination antibiotic therapy for MRSA bacteremia has not been shown to be more effective than single antimicrobial agent therapy. [Ref. 5.4: 04F8K2].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

A recent meta-analysis found substantial variation in the mortality rates (0%–83%) reported for SAB. [Ref. 5.4: 04FRZK] The wide variation in these mortality rates is likely attributable to differences in patient groups, settings, and the mortality measurements used. MRSA bacteremia was associated with significantly higher mortality rate than MSSA bacteremia. Mortality rates associated with SAB due to methicillin-resistant strains are particularly high among ICU patients [Ref. 5.4: 04FRZK] In a Belgian study that consisted of a subset of

critically ill patients, the MRSA bacteremia-associated mortality rate was 23.4%, which was significantly higher than the corresponding MSSA bacteremia-associated mortality rate of 1.3%. [Ref. 5.4: 04H0DG] An analysis of approximately 1,000 US hospitals revealed that inpatients with SAB had a 3-fold longer mean duration of hospital stay than did inpatients without SAB (14.3 vs. 4.5 days). [Ref. 5.4: 03Q0YJ]

Important co-morbidities:

- Diabetes mellitus
- Cardiovascular disease
- Renal impairment

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Background

The nonclinical safety profile of daptomycin has been well characterized in a comprehensive series of studies in adult and juvenile/neonatal animals that have defined the target organs of toxicity (skeletal muscle and peripheral nerve), the reversibility of changes, and the key parameters for clinical monitoring as reported in the Marketing Authorization Application to support the adult and pediatric cSSTI, SAB and infective endocarditis (SAB/IE) indications [Sec. 2.4] and [Sec. 2.6.1]. In addition, a series of reproductive and developmental studies in rats and rabbits were conducted. Long-term carcinogenicity studies in animals have not been conducted. Daptomycin was not mutagenic or clastogenic in a battery of *in vivo* and *in vitro* genotoxicity tests.

These data also supported the alternative administration of daptomycin over a two minute intravenous (IV) injection as an alternative to its administration as 30-minute IV infusion for adult patients [Sec. 2.7.2-adults2min].

The important non-clinical safety findings are summarized in [Table SII.1].

Important identified and potential risks are discussed in section [SVII.3].

[redacted]

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Single and repeat-dose toxicity: Daptomycin administration was associated with minimal to mild degenerative/regenerative changes in skeletal muscle in adult rats and dogs. Microscopic changes in skeletal muscle were minimal (approximately 0.05% of myofibers affected) and at the higher doses were accompanied by elevations in CPK in dogs. No fibrosis or rhabdomyolysis was observed. Depending on the study duration, all muscle effects, including microscopic changes, were fully reversible within 1-3 months following cessation of dosing. No functional or pathological changes in smooth or cardiac muscle were observed. Studies in dogs demonstrated that skeletal myopathy was related to the dosing frequency and AUC. In one study, the severity of myopathy was greater in dogs receiving daptomycin at a dose regimen of 25 mg/kg every 8 hours as compared with those receiving 25 or 75 mg/kg every 24 hours. In a second study in dogs, myopathy was similar at 25 mg/kg every 8 hours and at 100 mg/kg once daily, regimens that produced comparable AUC values. Data in dogs demonstrated a lack of skeletal myopathy correlated with daptomycin trough [Cmin (Minimum concentration)] plasma concentrations below approximately 25 µg/mL. The margin for the No Observed Adverse Effect Level (NOAEL) for skeletal myopathy in dogs (10 mg/kg) was based on AUC and was 0.8-fold greater than the clinical AUC at the adult therapeutic dose of 6mg/kg q24h. Effects on peripheral nerves were observed at higher doses than those associated with skeletal muscle effects in adult rats and dogs, and were primarily related to plasma Cmax (Maximum concentration). Peripheral nerve changes were characterized by minimal to slight axonal degeneration and were frequently accompanied by functional changes. Reversal of both the microscopic and functional effects was complete within 3 months post-dose. The safety margin for peripheral nerve effects in dogs is 5-fold based on comparison of Cmax values at the No Observed Adverse Effects Level (NOAEL) in dog of 25 mg/kg with the clinical Cmax achieved with the adult therapeutic dose of 6mg/kg q24h.	**Single and repeat-dose toxicity:** Increases in plasma CPK levels, muscular pains, weakness, and/or rhabdomyolysis have been reported during therapy with Cubicin. Peripheral neuropathy has been observed during post-marketing observations. Physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving Cubicin.
Genotoxicity: Daptomycin was not mutagenic, clastogenic or aneugenic in any of the in vitro or in vivo studies performed	**Genotoxicity:** Cubicin does not pose a genotoxic risk
Carcinogenicity: Carcinogenicity studies in animals have not been conducted	**Carcinogenicity:** No risk based on the short treatment duration and absence of genotoxicity in nonclinical in vitro and in vivo genotoxicity studies.
Reproductive Toxicity: Embryo/fetal development and teratology studies performed in rats and rabbits revealed no evidence of harm to the fetus due to daptomycin. The lack of embryo-fetal toxicity is consistent with autoradiographical data indicating minimal placental transfer of daptomycin to the fetus. In addition, peri- and postnatal assessments in the rat revealed no evidence of adverse effects on postnatal development or on the reproductive performance of the offspring. No studies have been conducted on the excretion of daptomycin in milk.	**Reproductive Toxicity:** There are no adequate and well-controlled studies of Cubicin in pregnant women. Because animal reproduction studies are not always predictive of human response, daptomycin should be used during pregnancy only if the expected benefit outweighs the possible risk. The postmarketing experience with daptomycin use during pregnancy is limited, and do not establish the presence or absence of drug-associated risk. There is no evidence to suggest that there is any increased risk for major birth defects or miscarriage following exposure to daptomycin. There were

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
However, oral bioavailability of daptomycin in adult rats is very low and no adverse effects were observed in nursing pups of female rats dosed through 21 days of lactation. While exposure was not assessed in the reproductive toxicology studies, the AUC following a single 75 mg/kg dose in rats (the NOAEL for embryo fetal development) was approximately 3-fold greater than the clinical AUC at the 6 mg/kg therapeutic dose. The AUC following a single 150 mg/kg dose in rats (the NOAEL for fertility, early embryonic development, and post-natal development) was approximately 10-fold greater than the clinical AUC at the 6 mg/kg adult therapeutic dose.	no adverse pregnancy outcomes reported for mothers or neonates in published reports containing information on the neonate's condition at delivery. There were no postmarketing reports of major birth defects associated with fetal exposure to daptomycin. The postmarketing clinical experience is limited and does not suggest an increased risk to the infant. Daptomycin is present in human milk but is poorly bioavailable orally. There is no information on the effects of daptomycin on milk production. In a single human case study, Cubicin was administered daily for 28 days to a nursing mother at an IV dose of 6.7 mg/kg/day, and samples of the patient's breast milk were collected over a 24-hour period on day 27. The highest measured concentration of daptomycin in the breast milk was 0.045 µg/mL, which is a low concentration. Therefore, based on this limited postmarketing experience with daptomycin exposure via lactation there is insufficient information to make a risk assessment for use in lactating women. There are no data on the effect of Cubicin on human fertility.
No impairment in fertility was demonstrated in studies in male and female rats.	
Toxicity in juvenile/neonatal 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. Following a 28-day recovery phase, microscopic examination revealed full recovery of the skeletal muscle and the ulnar nerve effects, and partial recovery of the sciatic nerve and spinal cord effects. No nerve effects were noted in juvenile dogs following 14 days of dosing. The No-Observed-Adverse-Effect-Level (NOAEL) in juvenile dogs was 20 mg/kg/day, which resulted in an AUC 0.6-fold greater, and a Cmax 1-fold greater than the clinical AUC and Cmax at the 6 mg/kg adult therapeutic dose. Effects of daptomycin were assessed in neonatal dogs following once-daily intravenous (iv) administration for 28 consecutive days from PND 4 through 31 at nominal dosage levels of 10 [no observed adverse effect level (NOAEL)], 25, 50 and 50/75 mg/kg/day. At dose levels of 50 and 75 mg/kg/day with associated Cmax and AUC_{inf} values of ≥321 microgram/mL and ≥1,470 microgram /mL, respectively, marked clinical signs	**Toxicity in juvenile/neonatal animals:** Pediatric patients below the age of one year should not be given Cubicin due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs at lower exposures than observed in adult or juvenile dogs. Safety of daptomycin for treatment of pediatric patients (1-17 years of age) for durations of up to 42 days has been studied in completed pediatric clinical trials. No evidence of effects on the peripheral or central nervous systems was observed in human clinical trials. Due to the juvenile dog and neonatal dog studies showing possible association of Cmax and nervous system toxicity, a longer infusion time is recommended for the administration of daptomycin to pediatric patients (at least 30-60 minutes). As shorter infusion times can increase the Cmax and the potential risk, daptomycin administration via two-minute injection has not been studied in pediatric patients. Unlike adults, the two-minute infusion time for daptomycin is not recommended for administration to pediatric patients.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
of twitching, muscle rigidity in the limbs, and impaired use of limbs were observed. Resulting decreases in body weights and overall body condition at dose ≥50mg/kg/day necessitated early discontinuation by PND19. At the dose level of 25 mg/kg/day associated Cmax and AUC_{inf} values of 147 microgram/mL and 717 microgram /mL, respectively, mild clinical signs of twitching and one incidence of muscle rigidity were observed without any effects on body weight and were reversible over a 28-days recovery period. These data indicate a limited margin between doses associated with mild versus marked adverse clinical signs. These clinical signs were possibly related to functional skeletal muscle and/or neurological (central nervous system or peripheral nerve) effects of daptomycin. Histopathological assessment did not reveal any daptomycin-related changes in the peripheral and central nervous system tissue, as well as in the skeletal muscle and tissue assessed, at any dose level. No adverse clinical signs for these target organs of toxicity were observed in the neonatal dogs that received daptomycin at 10 mg/kg/day, the NOAEL, with associated Cmax and AUCinf values of 62 microgram/ml and 247 microgram /mL, respectively. The neonatal Cmax and AUC at the NOAEL were approximately 0.6-fold and 0.5-fold greater, respectively, than the clinical Cmax and AUC at the 6 mg/kg therapeutic dose.	
General safety pharmacology: **Cardiovascular (including potential for QT interval prolongation):** No detectable treatment-related adverse effects were observed on heart rate, blood pressure, electrocardiogram (ECG) profile or QT interval *in vivo* in the dog following intravenous (iv) daptomycin doses up to 50 mg/kg (a C_{max} approximately 5-fold greater than the Cmax at the 6 mg/kg adult therapeutic dose). No effects were observed on isolated cardiac muscle, calcium ion flux in cardiac sarcoplasmic reticulum or potassium ion flux in cloned human ether-à-go-go related gene (hERG) channels at daptomycin concentrations up to 162 µg/mL, 128 µg/mL and 500 µg/mL, respectively.	**Cardiovascular (including potential for QT interval prolongation):** Hypertension, hypotension and supra-ventricular arrhythmia have been observed in patients administered Cubicin in clinical trials. Reviews of cardiac events in clinical trials and postmarketing experience, including a placebo-controlled study (DAP-QTNC-01-06 [Ref. 5.3.4.1: dapqtnc0106]) conducted to examine the effect of daptomycin on cardiac repolarization (QT interval), did not suggest any increased risk for QT prolongation or ventricular arrhythmias associated with daptomycin exposure. A separate cardiac safety evaluation is also available. [Sec. 2.7.4-adultsskin: 04ZMPB].
Mechanisms for drug interactions	None identified pre-clinically

Conclusions on Non-clinical Data

Following review of non-clinical studies, two concerns (severe skeletal muscle toxicity and peripheral neuropathy) were identified. Both concerns are adequately characterized in product labeling based on the cumulative clinical trial and postmarketing experience since initial approval in 2003, and no additional risk minimization measures or pharmacovigilance activities are warranted.

[redacted]

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Clinical Trial Exposure

Details on cumulative exposure to daptomycin in the clinical trials are given below. Overall, as of 19-JUN-2018, approximately 6277 patients have cumulatively been enrolled into the daptomycin clinical program of which approximately 3154 patients were exposed to daptomycin. This includes the ongoing study in Japan (MK3009-029, also known as P029) and completed studies sponsored by Novartis, Cubist and other license partners.

SIII.1.1 Ongoing Clinical Trials

There is one ongoing clinical trial enrolling pediatric patients with cSSTI or SAB as a voluntary study to support extending the marketing authorization in Japan (P029).

SIII.1.2 Completed Clinical Trials

The assessment of exposure was primarily based on patients from pooled studies completed until 19-JUN-2018 in adult and pediatric patients with cSSSI and SAB, as well as in healthy volunteers.

The total completed clinical trial population who received Cubicin at various doses of 4 mg, 6 mg, and greater than 6 mg daily encompass 2611 subjects including 455 pediatric patients. Out of this total experience with daptomycin, 4 groups can be defined to support the risk assessments for the targeted indications:

- 1162 cSSTI patients who received daptomycin. This includes 906 adult patients who received a dose of 4 mg/kg and 6 mg/kg (patients with concomitant bacteremia), 72 pediatric patients who received 5 mg/kg/day and 184 pediatric patients who received >6 mg/kg/day; 256 total pediatric cSSTI patients. (Included clinical studies: DAP-SST-98-01, DAP-SST-9801B, DAP-SST-99-01, DAP-PEDS-07-02, DAP-PEDS-07-03, DAP-RENSE-08-05, DAP-4HOME-09-05, DAP-4CELL-05-02, DAP-4PSW-03-03, and the Chiron/Novartis sponsored studies CBC134A2402, and CBC134A2404).

- 163 SAB/IE adult patients who received Cubicin at a dose of 6 mg/kg (patients with concomitant bacteremia) (Included clinical studies: DAP-IE-01-02, DAP4IE-06-03, and DAP-RENSE-08-05)

- 55 pediatric SAB patients who received daptomycin at a dose of 7 -12 mg/kg (clinical study:DAP-PEDBAC-11-02)

- 73 pediatric acute hematogenous osteomyelitis (AHO) patients who received daptomycin at a dose of 7 -12 mg/kg (clinical study: DAP-PEDOST-11-03).

The tabulations below describe the exposure for the indications included in this RMP and exposure is further broken down by number of subjects exposed to Cubicin by indication, duration of exposure [Table SIII.1.2.1 and SIII.1.2.2] and dose [Table SIII.1.2.3 and

[redacted]

SIII.1.2.4], exposure by age [Table SIII.1.2.5 and SIII.1.2.6], gender [Table SIII.1.2.7 and SIII.1.2.8], ethnicity/racial origin [Table SIII.1.2.9 and SIII.1.2.10] and special populations [Table SIII.1.2.11 and Table SIII.1.2.12].

Table SIII.1.2.1: Duration of Exposure in Adult Population (by Indication)

	Total trial population		cSSTI		SAB/IE	
Duration of exposure	**Persons[a]**	**Person time[b]**	**Persons[a]**	**Person time[b]**	**Persons[a]**	**Person time[b]**
≤ 14 days	1904	14608	837	6519	103	1033
> 14 days	251	6960	68	1334	60	1742
Missing	1	-	1	-	0	-

[a] Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSTI and SAB/IE populations.

[b] Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category. For subjects with renal impairment who are dosed 3 times per week (3Xweek), once every 48 hours (Q48H), or once every 24 hours (Q24H) enrolled in the DAP-RENSE-08-05 study, the number of dosing days was used instead of duration.

[redacted]

Table SIII.1.2.2: Duration of Exposure in Pediatric Population (By Indication) (Safety Population - All Pediatric Studies)

	Total trial population		cSSSI		SAB		Other Study	
Duration of Exposure	Persons	Person time	Persons	Person time	Persons	Person time	Persons	Person time
≤ 14 days	412	1696	256	914	37	298	58	423
15 - 27 days	25	462	0	0	15	274	10	188
≥ 28 days	9	333	0	0	3	101	6	232

cSSSI: complicated skin and skin structure infections; SAB: Staphylococcus aureus bacteremia.

- Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSSI, SAB and Other Study populations.
- Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category

Note: Total trial population Studies included: DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-07-03, DAP-PEDS-09-01, DAP-PEDBAC-11-02, and DAP-PEDOST-11-03.

cSSSI = DAP-PEDS-07-03; SAB = DAP-PEDBAC-11-02; Other Study = DAP-PEDOST-11-03 in acute hematogenous osteomyelitis (AHO: unapproved indication).

Table SIII.1.2.3: Exposure by Dose in Adult Population (by Indication)

	Total trial population		cSSTI		SAB/IE	
Duration of exposure	Persons[a]	Person time[b]	Persons[a]	Person time[b]	Persons[a]	Person time[b]
<4 mg/kg per day	0	-	0	-	0	-
4 mg/kg per day	1558	12886	902	7793	0	-
5 mg/kg per day	72	319	72	319	0	-
6 mg/kg per day	494	7213	4	69	163	2775
>6 mg/kg per day	104	1477	0	-	0	-

[a] Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSTI and SAB/IE populations.

[b] Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category. For subjects with renal impairment who are dosed 3 times per week (3Xweek), once every 48 hours (Q48H), or once every 24 hours (Q24H) enrolled in the DAP-RENSE- 08-05 study, the number of dosing days was used instead of duration.

[redacted]

Table SIII.1.2.4: Exposure by Dose in Pediatric Population (By Indication) (Safety Population - All Pediatric Studies)

	Total trial population		cSSSI		SAB		Other Study	
Duration of Exposure	Persons	Person time	Persons	Person time	Persons	Person time	Persons	Person time
≤ 6 mg/kg per day	121	368	72	319	0	0	0	0
7-9 mg/kg per day	244	1536	154	531	33	384	51	615
≥ 10 mg/kg per day	81	587	30	64	22	289	23	228

cSSSI: complicated skin and skin structure infections; SAB: Staphylococcus aureus bacteremia.

- Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSSI, SAB and Other study populations.
- Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category

Note: Total trial population Studies included: DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-07-03, DAP-PEDS-09-01, DAP-PEDBAC-11-02, and DAP-PEDOST-11-03.
cSSSI = DAP-PEDS-07-03; SAB = DAP-PEDBAC-11-02; Other Study= DAP-PEDOST-11-03.

[redacted]

Table SIII.1.2.5: Exposure by Age in Adult Population (by Indication)

	Total trial population		cSSTI		SAB/IE	
Age	Persons[a]	Person time (day)[b]	Persons[a]	Person time (day)[b]	Persons[a]	Person time (day)[b]
< 65 years	1480	14762	593	5017	127	2299
>= 65 years	669	6809	313	2844	36	476
Missing	7	7	0	-	0	-

[a] Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSTI and SAB/IE populations.

[b] Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category. For subjects with renal impairment who are dosed 3 times per week (3Xweek), once every 48 hours (Q48H), or once every 24 hours (Q24H) enrolled in the DAP-RENSE- 08-05 study, the number of dosing days was used instead of duration.

[redacted]

Table SIII.1.2.6: Exposure by Age in Pediatric Population (By Indication) (Safety Population - All Pediatric Studies)

	Total trial population		cSSSI		SAB		Other Study	
Age	Persons	Person time	Persons	Person time	Persons	Person time	Persons	Person time
< 2 years	58	113	30	64	0	0	4	25
2 to <7 years	144	694	81	170	22	289	20	214
7 to <12 years	125	839	73	361	19	206	25	264
12 to <18 years	119	845	72	319	14	178	25	340

cSSSI: complicated skin and skin structure infections; SAB: Staphylococcus aureus bacteremia.

- Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSSI, SAB and Other Study populations.
- Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category

Note: Total trial population Studies included: DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-07-03, DAP-PEDS-09-01, DAP-PEDBAC-11-02, and DAP-PEDOST-11-03.
cSSSI = DAP-PEDS-07-03; SAB = DAP-PEDBAC-11-02; Other Study = DAP-PEDOST-11-03.

Table SIII.1.2.7: Exposure by Gender in Adult Population (by Indication)

	Total trial population		cSSTI		SAB/IE	
Gender	Persons[a]	Person time (day)[b]	Persons[a]	Person time (day)[b]	Persons[a]	Person time (day)[b]
Male	1191	12027	475	4141	96	1586
Female	965	9951	431	3721	67	1189

[a] Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSTI and SAB/IE populations.

[b] Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category. For subjects with renal impairment who are dosed 3 times per week (3Xweek), once every 48 hours (Q48H), or once every 24 hours (Q24H) enrolled in the DAP-RENSE-08-05 study, the number of dosing days was used instead of duration.

[redacted]

Table SIII.1.2.8: Exposure by Gender in Pediatric Population (By Indication) (Safety Population - All Pediatric Studies)

	Total trial population		cSSSI		SAB		Other Study	
Gender	Persons	Person time	Persons	Person time	Persons	Person time	Persons	Person time
Male	238	1576	130	511	38	461	43	577
Female	208	915	126	403	17	212	31	266

cSSSI: complicated skin and skin structure infections; SAB: Staphylococcus aureus bacteremia.

- Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSSI, SAB and Other Study populations.
- Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category

Note: Total trial population Studies included: DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-07-03, DAP-PEDS-09-01, DAP-PEDBAC-11-02, and DAP-PEDOST-11-03.
cSSSI = DAP-PEDS-07-03; SAB = DAP-PEDBAC-11-02;Other Study = DAP-PEDOST-11-03.

Table SIII.1.2.9: Exposure by Ethnicity in Adult Population (by Indication)

	Total trial population		cSSTI		SAB/IE	
Ethnicity	Persons[a]	Person time (day)[b]	Persons[a]	Person time (day)[b]	Persons[a]	Person time (day)[b]
American Indian or Alaska Native	2	7	0	-	0	-
Asian	20	190	4	41	3	50
Black	367	3605	176	1297	45	1062
Caucasian	1359	12664	579	5071	75	1121
Hispanic/Latino	0	-	0	-	0	-
White	91	2267	15	157	28	329
Other	277	2322	92	774	12	213
Missing	40	526	40	526	0	-

[a] Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSTI and SAB/IE populations.

[b] Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category. For subjects with renal impairment who are dosed 3 times per week (3Xweek), once every 48 hours (Q48H), or once every 24 hours (Q24H) enrolled in the DAP-RENSE-08-05 study, the number of dosing days was used instead of duration.

[redacted]

Table SIII.1.2.10: Exposure by Race in Pediatric Population (By Indication) (Safety Population - All Pediatric Studies)

Race	Total trial population		cSSSI		SAB		Other Study	
	Persons	Person time	Persons	Person time	Persons	Person time	Persons	Person time
American Indian or Alaska Native	2	2	0	0	0	0	0	0
Asian	86	554	83	532	2	16	1	6
Black or African American	98	290	64	137	6	58	10	77
Native Hawaiian or Other Pacific Islander	1	1	0	0	0	0	0	0
White	246	1584	104	237	43	553	62	757
Other	13	60	5	8	4	46	1	3

cSSSI: complicated skin and skin structure infections; SAB: Staphylococcus aureus bacteremia.

- Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSSI, SAB and Other Study populations.
- Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category

Note: Total trial population Studies included: DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-07-03, DAP-PEDS-09-01, DAP-PEDBAC-11-02, and DAP-PEDOST-11-03.
cSSSI = DAP-PEDS-07-03; SAB = DAP-PEDBAC-11-02; Other Study = DAP-PEDOST-11-03.

[redacted]

Table SIII.1.2.11: Exposure in Special Adult Population: Renal Impairment (by Indication)

	Total trial population		cSSTI		SAB/IE	
Population	Persons[a]	Person time (day)[b]	Persons[a]	Person time (day)[b]	Persons[a]	Person time (day)[b]
Hemodialysis/CAPD	89	1056	15	189	14	207
CrCl < 30 mL/min	34	224	9	60	5	41
CrCl 30 - <50 mL/min	190	1811	60	504	22	323
CrCl 50 - 80 mL/min	467	4496	146	1238	39	581
CrCl > 80 mL/min	1171	11781	521	4510	83	1623
CrCl unknown	205	2211	155	1361	0	-

[a] Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSTI and SAB/IE populations.

[b] Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category. For subjects with renal impairment who are dosed 3 times per week (3Xweek), once every 48 hours (Q48H), or once every 24 hours (Q24H) enrolled in the DAP-RENSE- 08-05 study, the number of dosing days was used instead of duration.
CAPD: Continuous Ambulatory Peritoneal Dialysis
CrCl: Creatinine clearance

Table SIII.1.2.12: Exposure in Special Pediatric Population: Renal Impairment (By Indication) (Safety Population - All Pediatric Studies)

Population	Total trial population		cSSSI		SAB		Other Study	
	Persons	Person time	Persons	Person time	Persons	Person time	Persons	Person time
Haemodialysis/CAPD	0	0	0	0	0	0	0	0
CrCl < 30 mL/min	1	8	1	8	0	0	0	0
CrCl 30 - <50 mL/min	3	17	3	17	0	0	0	0
CrCl 50 - 80 mL/min	73	500	54	283	5	59	11	155
CrCl> 80 mL/min	363	1948	194	598	49	613	62	679
CrCl unknown	6	18	4	8	1	1	1	9

cSSSI: complicated skin and skin structure infections; CAPD: continuous ambulatory peritoneal dialysis; CrCl: Creatinine Clearance;
SAB: Staphylococcus aureus bacteremia.

- Persons include patients and healthy volunteers in the total trial population, but only patients in the cSSSI, SAB and Other Study populations.
- Person time was calculated by multiplication of the number of persons with the mean IV treatment duration (days) in each category

Note: Total trial population Studies included: DAP-PEDS-05-01, DAP-PEDS-07-02, DAP-PEDS-07-03, DAP-PEDS-09-01, DAP-PEDBAC-11-02, and DAP-PEDOST-11-03.
cSSSI = DAP-PEDS-07-03; SAB = DAP-PEDBAC-11-02; Other Study= DAP-PEDOST-11-03.
Dialysis/CAPD were exclusionary criteria

[redacted]

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Pregnant or lactating women	Embryo-fetal development studies performed in rats and rabbits revealed no evidence of harm to the fetus due to daptomycin. Daptomycin can cross the placenta in pregnant rats. Daptomycin has been detected in low concentrations in human breast milk in a single human case study. Oral absorption of daptomycin from breast milk is expected to be poor.	No	There are no adequate and well-controlled studies of daptomycin in pregnant women or in breastfeeding mothers and their infants. Clinical use of daptomycin during pregnancy or lactation is anticipated to be unusual in postmarketing experience (see section SIV.4). Alternative therapies are available. Product labeling advises that daptomycin should be used during pregnancy or during breast feeding only if the potential benefit outweighs the possible risks.
Hepatic impairment	The pharmacokinetics of daptomycin were not altered in subjects with mild or moderate hepatic impairment. The PK of daptomycin in patients with severe hepatic impairment has not been evaluated.	No	No dosage adjustment is warranted when daptomycin is administered to patients with mild to moderate hepatic impairment (Child-Pugh Class B). No dosing recommendations can be made for patients with severe hepatic impairment.
Renal impairment	Daptomycin is eliminated primarily by the kidney.	No	Dosing recommendations for adult patients with renal impairment (including dialysis patients) are included in the labeling and based on completed PK studies. PK in pediatric patients with renal impairment has not been studied. Dosage adjustment for pediatric patients with renal impairment has not been established. Clinical use of daptomycin for pediatric patients with renal impairment is not anticipated to occur as other alternative therapies are available. No further studies are planned for pediatric patients with severe renal impairment.

[redacted]

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Pregnant and lactating women were not studied in clinical trials. 36 post-marketing reports of use during pregnancy* 13 postmarketing reports of exposure during lactation*
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	Hepatic impairment clinical trial subjects: 10 subjects who had moderate hepatic impairment (Child-Pugh B classification); no subjects were enrolled who had severe hepatic impairment (Child-Pugh C classification) Renal impairment pediatric clinical trial subjects (CrCL≤ 80 ml/min): 66 Renal impairment adult clinical trial subjects (CrCL≤ 80 ml/min):780

* Postmarketing data up to 11-SEP-2018

Pregnant or breast feeding women

Pregnancy and lactation were exclusion criteria in the entire clinical development program. There are no human clinical data from controlled clinical trials or pregnancy registry to evaluate the risk associated with exposure to daptomycin during pregnancy or breast-feeding. There is no pregnancy registry for CUBICIN. The available sources of human clinical safety data for pregnant or breastfeeding women are comprised of postmarketing spontaneous reports and published literature reports which are reviewed and summarized in section SV.

Patients with hepatic impairment

No data are available in patients with severe hepatic impairment (Child-Pugh Class C). The PK of daptomycin in patients with severe hepatic impairment has not been evaluated.

Metabolism of daptomycin does not occur to any detectable extent in the liver and, therefore, hepatic impairment would not be expected to reduce clearance. This was confirmed in a

study (DAP-HEP-00-09) comparing PK parameters in 10 subjects who had moderate hepatic impairment (Child-Pugh B classification) with those of 9 healthy subjects, all receiving a 6 mg/kg single dose of daptomycin.

Patients with renal impairment

Adults with cSSTI, Dose 4 mg/kg

Patients with severe renal impairment (CrCl <30ml/min) were excluded from clinical trials in patients with infections. However, patients with severe renal impairment were investigated in PK studies. Patients with mild to moderate renal impairment (CrCl 30 to 60 ml/min) were included in studies as described below.

The studies conducted for renal impaired patients so far, demonstrate that systemic exposures following a 4 mg/kg dose for treatment of cSSTI in subjects with normal renal function and mild or moderate renal impairment are comparable. Therefore, dose adjustment is not necessary in these subjects as it may be more likely to expose the patient to reduced clinical efficacy due to suboptimal AUC and Cmax.

However, a significant increase in exposure to daptomycin, measured by AUC, is observed in subjects with severe renal impairment (CrCl < 30mL/min) or ESRD. Consequently, the dosing interval should be extended from once daily dosing to once every other day dosing in patients with severe renal impairment treated for cSSTI and for patients on hemodialysis or CAPD. Whenever possible, daptomycin should be administered following the completion of dialysis on dialysis days.

Adults with SAB, Dose 6 mg/kg

Based on data from study DAP-4REN-03-06, from the clinical PK study DAP-REN-07-01, from the review of all PK data available for daptomycin in renal impaired patients and from the data of post-marketing analyses from the Cubicin Outcomes Registries in the US and EU (CORE, and EU-CORE), the CCDS recommends a dose adjustment for bacteremia subjects with severe renal impairment (CrCl < 30mL/min) or ESRD, with a dosing interval modified from once daily to once every other day dosing, aligning with the recommendations provided for the treatment of cSSTI.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

Pneumonia

Cubicin is not indicated for the treatment of pneumonia. It has been demonstrated in clinical studies that daptomycin is not effective in the treatment of community-acquired pneumonia (inhalational or airborne pneumonia), due to binding to pulmonary surfactant and consequent inactivation.

[redacted]

Patients of different racial and/or ethnic origin

The patient populations recruited for the daptomycin development program were mainly Caucasian (approximately 61% of adults and pediatric patients) with approximately 18% Black patients included among the total study population. Limited data are available for other racial/ethnic groups – see previous section [Table SIII.1.2.8] and [Table SIII.1.2.9].

One PK study has been conducted in the Chinese population (DAP-CHPK-07-04). The study was an evaluation of the PK profile and safety of single and multiple doses of daptomycin, 6 mg/kg, in healthy subjects of Chinese ethnicity who lived in the United States. The conclusion of this study indicated that single and multiple doses of daptomycin were safe and well tolerated in subjects of Chinese ethnicity. The PK profile of single-dose and multiple-dose daptomycin 6 mg/kg IV in subjects of Chinese ethnicity was similar to that reported in previous studies of daptomycin 6 mg/kg in adult subjects of other ethnicities.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Worldwide patient exposure for daptomycin (Cubicin and Cubicin RF[1]) for the period 12-SEP-2003 (IBD) to 11-SEP-2018 was estimated from quarterly unit sales data provided by the IQVIA MIDAS Quantum database. Data from all business partners (Merck, Astra Zeneca, CC Pharma, Novartis and TTY Biopharm Company Limited) is included and broken out by product, dose, and country. IQVIA maintains 12 years of rolling quarterly sales data in its Quantum database. This consists of international data covering 70+ countries. Data is sourced primarily from Retail and Hospital sales collected from wholesalers, pharmacies and hospitals. For time periods not currently captured in the Quantum database, it is standard practice for IQVIA to obtain the unit distribution exposure per day from a known time period and apply that exposure rate to the unknown period. If current exposure is considerably more (or less) than the actual exposure in the unknown periods the estimates could be skewed high (or low) and are presented below in section **SV.1.2** below.

Although approvals have been granted in some countries for the 250 mg vial, only the 350 mg and 500 mg vials are commercially available at the current time. In the US, both Cubicin and Cubicin RF 500 mg vials were commercially available during the reporting period; IMS data were obtained for Cubicin RF for the period from launch (05-AUG-2016) to the last data available for the DLP for the last periodic safety report (11-SEP-2018). The methodology for estimating the number of patients treated with daptomycin in the MSD territories (e.g. US, Canada, Israel, etc) and business partner territories takes into account the actual vials of daptomycin sold to date, as well as the assumptions for average dose and average duration of therapy. The average dose assumption is based on grams per day obtained from market research (for the US, from Arlington Medical Resources (AMR)). The average duration assumption is derived from the average duration of treatment employed in the cSSSI and SAB/RIE clinical trials and is then weighted by the infection category mix (skin, systemic, or other) reported by AMR. The average dose and duration assumptions have not been modified since the last PSUR (DLP 11-SEP-2017). There are no data currently available to evaluate potential differences in the usage patterns for Cubicin RF.

The estimate of vials used per patient per treatment course for this reporting period is the same as that of the previous reporting periods, approximately 12.1 vials per patient per treatment course for the US and countries other than the EU. The average duration of treatment for the approved indications in the EU remains at 9.5 days and therefore, the resulting number of vials per patient per treatment course is estimated at 9.5. For the region of Taiwan, where TTY Biopharm Company Limited is the license holder, the number of vials per patient per treatment course is estimated at 21, based on the approved indications for daptomycin treatment of bacteraemia or complicated skin infection, and the average

[1] Cubicin RF is a reformulation of daptomycin in a room-temperature stable lyophilized powder in single-use vials. Cubicin RF is not available in the EEA.

[redacted]

treatment period for a patient with these infections was about 21 days. The clinical trial experience in the approved indications would imply theoretical lower and upper limits of treatment courses, ranging from 7 days (cSSTI) to 42 days (for SAB/RIE). The estimated patient exposure was based upon assumption that 1 vial is equivalent to one patient treatment day; the total patient years of treatment is derived from total patient days divided by 365.25.

SV.1.2 Exposure

For the cumulative period from the IBD to 11-SEP-2018, **45,846,512** vials of CUBICIN and CUBICIN RF were sold. Cumulative patient exposure is estimated to be **3,950,752** patients, or **125,521** patient treatment years (PTY).

Table SV.1.2.1: Cumulative Patient Exposure of Daptomycin from Worldwide Marketing Experience from 12-SEP-2003 to 11-SEP-2018

Product	Dose	Units	PTY	Patients
CUBICIN	350MG	6,318,596	17,299	608,096
	500MG	38,598,890	105,678	3,265,877
	Total	**44,917,486**	**122,977**	**3,873,973**
CUBICIN RF	500MG	929,026	2,544	76,779
	Total	**929,026**	**2,544**	**76,779**
Overall Total		**45,846,512**	**125,521**	**3,950,752**

[redacted]

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

No risk minimization is required due to the absence of psychotropic effects.

[redacted]

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

The list of safety concerns for daptomycin as listed in EU RMP version 10.2 was re-evaluated with aggregate postmarketing and clinical trial safety data based upon the guidance provide in GVP Mod V (rev 2) from the IBD (12-SEP-2003) through 11-SEP-2018. Routine risk minimization measures (i.e. product labeling) are appropriate to maintain a positive benefit to risk balance for use of Cubicin for the targeted indications. Routine pharmacovigilance, namely through signal detection and adverse reaction reporting in periodic update reports, will continue to follow up on these areas for any changes in the risk profile requiring an update to safety labeling or additional risk minimization measures. No additional PV activities are planned as the risks have been well characterized during more than 14 years of postmarketing experience and over 44 million patient doses. Results of a survey by Novartis (the former MAH in the EU) to physicians on the effectiveness of the ARMMs (laboratory testing guide and dosing card) were submitted to EMA in January 2012 and no additional follow-up was requested by EMA.

Important Identified Risks that are being removed:

Severe skeletal muscle toxicity: previously classified as an important identified risk is now removed from the list of safety concerns. This concern is fully characterized and appropriately managed in the product labeling. The product labeling provides Warnings and Precautions with recommendations on monitoring of signs and symptoms of skeletal muscle toxicity, and on how often CPK levels should be measured during therapy, and the Adverse Reactions section also includes elevated CPK, muscle pain, limb pain, muscle weakness, myoglobin increased, and rhabdomyolysis as expected ADRs. Specific clinical measures to mitigate the risk have become fully integrated into standard clinical practice, such as additional monitoring of blood CPK levels and recommended levels for interrupting or discontinuation of therapy. Therefore, there is no need for additional risk minimization measures. The educational material for prescribers (Dosing Guide) which was deployed under EU RMP v10.2 is being retired from this RMP.

[redacted]

Reduced susceptibility to daptomycin in *S. aureus* (includes both *Staphylococcus aureus* and *Enterococcus* species): previously classified as an important identified risk is now removed from the list of safety concerns. There are no additional PV activities planned as the risk for decreased susceptibility to daptomycin has been well characterized in postmarketing experience since the first marketing approval in 2003 through the completion of surveillance studies in the US and EU (final surveillance studies were completed in Japan in 2017). Routine PV activities have revealed the risk-benefit profile to remain favorable for the target indications and listed susceptible pathogens. There are clinical trial data to support the efficacy of the proposed regimen of daptomycin for treatment of cSSTI where susceptible strains of *Enterococcus faecalis* (vancomycin-susceptible strains) are isolated. However, in postmarketing experience, there have been reports of treatment failures with daptomycin for the treatment of enterococcal infections that were mostly accompanied by bacteraemia, which may require doses higher than the recommended therapeutic regimen for cSSSI. In some instances, treatment failure has been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin. Guidelines for susceptibility testing and interpretation of in vitro testing results have been integrated in the standard practice guidelines for antimicrobial products maintained by external experts (European Committee on Antimicrobial Susceptibility testing, EUCAST, and Clinical and Laboratory Standards Institute, CLSI). In June 2018, CLSI revised interpretive breakpoints for enterococcal infections due to the emergence of multiple published reports of treatment failures associated with clinical isolates of *Enterococcus* species with MIC > 1 mg/L. Therefore, no additional risk minimization measures are warranted. The educational material for health care professionals (Antimicrobial Susceptibility Testing Guide for Laboratories) which was deployed under EU RMP v10.2 is being retired from this RMP.

Peripheral neuropathy: previously classified as an important identified risk is now removed from the list of safety concerns. The nature of this risk has been adequately characterized in product labeling, and routine risk minimization measures remain appropriate for maintaining the positive benefit to risk profile for product use in the targeted indications. The product labeling contains appropriate Warnings and Precautions, including advice that pediatric patients younger than one year old should not be given Cubicin due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs. The product labeling also contains the signs/symptoms of neuropathy (e.g. paresthesia, muscular weakness, limb pain) which are listed as Adverse Reactions. No additional risk minimization activities are warranted.

Hypersensitivity reactions (including pulmonary eosinophilia and severe cutaneous reactions including acute generalized exanthematous pustulosis, AGEP): previously classified as an important identified risk is now removed from the list of safety concerns. This safety concern has been adequately characterized in product labeling, and routine risk minimization measures remain appropriate for maintaining the positive benefit to risk profile for product use in the targeted indications. Product labeling contains Warnings & Precautions for Anaphylaxis and Hypersensitivity Reactions, and the listed adverse reactions also contain a description of Hypersensitivity reactions, including, but not limited to, anaphylaxis, angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), and pulmonary eosinophilia, as well as severe cutaneous reactions: vesicobullous rash with

mucous membrane involvement, and AGEP. No additional pharmacovigilance activities are planned or ongoing. No additional risk minimization activities are warranted.

Eosinophilic pneumonia: previously classified as an important identified risk is now removed from the list of safety concerns. This safety concern has been adequately characterized in product labeling, including Warnings & Precautions describing the postmarketing experiences associated with Cubicin. Prescribers are provided with a description of the clinical presentation (e.g. fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organizing pneumonia), the anticipated clinical course, and recommended interventions to mitigate this risk. The current labeling also contains: cough, eosinophilic pneumonia, and organizing pneumonia as adverse reactions (Undesirable Effects section). Routine risk minimization measures remain appropriate for maintaining the positive benefit to risk profile for product use in the targeted indications.

Important Potential Risks that are being removed:

No additional PV activities are planned as these risks have been extensively evaluated and the cumulative experience to date does not support that there is a causal association to daptomycin. No additional risk minimization activities are planned. Routine risk minimization (in product labeling) remains appropriate for maintaining the positive benefit to risk profile for product use in the targeted indications and informing prescribers on the observed adverse reactions in clinical trials and postmarketing experience. These concerns will continue to be evaluated through routine pharmacovigilance activities, namely as part of signaling activities and in periodic safety update reports.

Bone marrow toxicity: previously classified as an important potential risk is now removed from the list of safety concerns. Scientific and clinical data do not support the initial supposition that hematologic disorders and laboratory changes observed in clinical trials and postmarketing experience are causally associated with daptomycin. Nonclinical toxicology studies did not indicate a primary or direct effect of daptomycin on bone marrow function, therefore there is no scientific basis to anticipate bone marrow toxicity. The adverse reaction terms of anaemia and thrombocytopenia are included in product labeling based on evaluation of clinical trial and postmarketing experience, but there is no evidence to support that these reactions were direct adverse effects of daptomycin on bone marrow function.

Severe hepatotoxicity: previously classified as an important potential risk is now removed from the list of safety concerns. Nonclinical and clinical data do not support the initial supposition that severe hepatotoxicity is causally associated with daptomycin. Daptomycin is not metabolized or cleared to any significant extent by the liver. Liver function tests may show alterations beginning in the early stages of bacteraemia and sepsis, indications for treatment which also confounded assessment in a large proportion of cases reported in clinical trials and postmarketing experience. Increased AST and/or ALT values were seen in relation to signs and symptoms of skeletal muscle injury and elevations in CPK in some reports, which may represent a skeletal muscle source rather than liver injury. Overall the number of reports of severe hepatotoxicity in postmarketing experience remains low,

suggesting that the impact to patients is less than anticipated at the time of original marketing approval. There is no reasonable expectation that any pharmacovigilance activity can further characterize the risk for severe hepatotoxicity. Product labeling contains information on the expected adverse reactions including liver function test abnormalities (increased ALT, AST, or alkaline phosphatase) and jaundice.

Dysregulation of in vivo coagulation; This important potential risk was added to the EU RMP in 2010 following the results of an investigation into postmarketing reports of prolonged prothrombin time (PT) and increased international normalized ratio (INR) using certain recombinant thromboplastin reagents. The interference between daptomycin and specific reagents used in some PT/INR assays lead to false results, with apparent prolongation of PT and elevation of INR. The potential for erroneous results may be minimized by drawing samples near the time of daptomycin trough plasma concentration. This item is appropriately communicated through the SmPC (Section 4.4: Special warnings and precautions for use and Section 4.5: Interaction with other medicinal products and other forms of interaction) with a labeling update in 2010. In a cumulative review of clinical trial and postmarketing experience through 11-SEP 2018, there has been no evidence to suggest that daptomycin is causally associated with dysregulation of coagulation in vivo. The current SmPC contains appropriate language to advise health care professionals on how to manage this interaction when monitoring patients receiving concomitant daptomycin and anticoagulant therapy. The undesirable effects section also lists Prothrombin time prolonged and INR increased as expected adverse reactions. No additional risk minimization measures are required to inform prescribers of this safety concern. No additional pharmacovigilance activities are planned, and routine surveillance will evaluate and report any significant new information on this concern.

Missing Information that is being removed:

Pregnancy and Lactation: previously classified as missing information is now removed from the list of safety concerns. There are no available data from pregnancy registries or other studies of daptomycin use during pregnancy or lactation. The available sources of human clinical safety data are comprised of postmarketing spontaneous reports and published literature reports from the IBD through 11-SEP-2018. Reviews of the cumulative postmarketing experience and the published literature described below have not revealed any safety concerns. The risk is reduced by routine risk minimization measures (i.e. pregnancy and lactation risk assessments that are appropriately included in the product labeling). No additional risk minimization activities are planned as these routine measures are considered to be sufficient to inform prescribers of the risks for exposure during pregnancy or lactation. The use of daptomycin in pregnant or breastfeeding women is anticipated to be very low based on postmarketing reports received. The current risk minimization measures appear effective to maintain the overall positive benefit to risk profile.

Pregnancy

In cumulative postmarketing experience from the IBD to 11-SEP-2018, a total of 36 spontaneous reports of exposure during pregnancy have been received. None of the

[redacted]

spontaneous postmarketing reports contained evidence of major birth defects. There was one spontaneous report of miscarriage following exposure to daptomycin, with limited information on the timing of daptomycin exposure and potential contributing factors. Of the six published reports describing daptomycin exposure during pregnancy, five cases described pregnancy exposure during the third trimester and one case described exposure in the late second trimester. There is no published information on experience with daptomycin during earlier stages of pregnancy. The single published case report that described adverse events of premature birth and low birth weight was attributable to emergency delivery due to maternal distress as a complication of MRSA osteomyelitis (the indication for treatment with daptomycin) and was not attributed by the authors to daptomycin [Ref. 5.4: 04HV3B].

The postmarketing experience with daptomycin use during pregnancy is limited and does not establish the presence or absence of drug-associated risk. There is no evidence to suggest that there is any increased risk for major birth defects or miscarriage following exposure to daptomycin. There were no adverse pregnancy outcomes reported for mothers or neonates in published reports containing information on the neonate's condition at delivery. There were no postmarketing reports of major birth defects associated with fetal exposure to daptomycin.

Lactation

Since the IBD of daptomycin to 11-SEP-2018, a total of 13 reports of exposure to daptomycin via lactation have been received. No AEs were reported in any of the breast-fed babies. Two published case reports were identified which described exposure to daptomycin during lactation and provided additional pharmacokinetic data on daptomycin excretion in breast milk [Ref. 5.4: 04H0DP] and [Ref. 5.4: 04ZB0V]. The analyses in each of these case reports showed that daptomycin is excreted into human breast milk at very low concentrations compared to maternal plasma (0.32 mcg/ml and 44.7 ng/ml [0.045 mcg/mL] as the maximum values observed in breast milk; and 0.05 as the maximum milk-plasma concentration ratio reported) with no adverse effects reported in the exposed infants in either case report. No new safety concerns were identified.

The postmarketing clinical experience is limited and does not suggest an increased risk to the infant. Daptomycin is present in human milk but is poorly bioavailable orally. Therefore, based on this limited postmarketing experience with daptomycin exposure via lactation, there is insufficient information to make a risk assessment for use in lactating women.

Patients with Hepatic Impairment: The safety of daptomycin in patients with hepatic impairment is also no longer considered missing information. Routine risk minimization includes product labeling which describes the limitations to clinical experience in patients with severe hepatic impairment, and that dose adjustments are not warranted in patients with mild or moderate hepatic impairment. Review of the postmarketing experience has confirmed that these measures appear to be adequate and has not revealed any safety concerns for this patient population. No additional risk minimisation activities are planned as

the anticipated usage in patients with severe hepatic impairment is expected to be very low. The MAH will continue to monitor cases of patients with hepatic impairment to assess for any new important safety concerns.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no identified risks, potential risks, or missing information in this RMP.

SVII.3.2 Presentation of the Missing Information

There is no missing information for daptomycin.

[redacted]

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

[redacted]

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-Up Questionnaires for Safety Concerns:

Not applicable.

The MAH will no longer use targeted follow-up questionnaires, as all of the safety concerns have been retired.

Other Forms of Routine Pharmacovigilance Activities for Safety Concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities proposed for daptomycin.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

[redacted]

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There is one ongoing clinical trial enrolling pediatric patients with cSSTI or SAB (P029) as a voluntary study to support extending the marketing authorization in Japan. This safety and efficacy study is not required as a condition of a marketing authorization nor is it a specific obligation under a marketing authorization. Therefore, it is not included in Annex 5.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed prescribing information is aligned to the reference medicinal product.

V.1 Routine Risk Minimization Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
None	Not applicable

V.2 Additional Risk Minimization Measures

Not applicable

V.3 Summary of Risk Minimization Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
None	Not applicable	Not applicable

[redacted]

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for daptomycin (CUBICIN)

This is a summary of the risk management plan (RMP) for daptomycin (CUBICIN). The RMP details important risks of daptomycin, how these risks can be minimized, and how more information will be obtained about the risks and uncertainties (missing information) for use of daptomycin.

Daptomycin's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how daptomycin should be used.

This summary of the RMP for daptomycin should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of daptomycin's RMP.

I. The Medicine and What it is Used for

Daptomycin is authorized for the treatment of complicated skin and soft tissue infections (cSSTI), *Staphylococcus aureus* bacteraemia (SAB) when associated with cSSTI in adults and pediatric patients (1 to 17 years of age) and right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* in adults (see SmPC for the full indication). It contains daptomycin as the active substance and it is given by intravenous infusion.

Further information about the evaluation of daptomycin's benefits can be found in daptomycin's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/documents/overview/Cubicin-epar-summary-public_en.pdf

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of daptomycin, together with measures to minimise such risks and the proposed studies for learning more about the risks associated with daptomycin risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet (where applicable) and product labeling addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of daptomycin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of daptomycin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

The safety information in the Summary of Product Characteristics is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of daptomycin.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for daptomycin.

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ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable