Cubicin

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
N/0088	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/06/2024		PL	
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/12/2022		PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

IB/0085/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	03/11/2022	n/a		
IB/0084/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	15/09/2022	n/a		

IA/0086	B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised	30/08/2022	n/a		
IA/0083	A.7 - Administrative change - Deletion of manufacturing sites	09/06/2022	n/a		
WS/2193	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	02/06/2022	n/a		
PSUSA/931/202109	Periodic Safety Update EU Single assessment - daptomycin	05/05/2022	n/a		PRAC Recommendation - maintenance
IA/0082/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	21/12/2021	n/a		
IA/0079	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	06/10/2021	n/a		

IAIN/0078	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	22/09/2021	14/02/2022	SmPC and PL	
IA/0077	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	14/07/2021	n/a		
IAIN/0076/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	15/02/2021	14/02/2022	Annex II and PL	
II/0075	Update of sections 4.4 and 4.8 of the SmPC in order to include two new terms, tubulointerstitial nephritis (TIN) and drug reaction with eosinophilia and systemic symptoms (DRESS) to the Special warnings and precautions of the SmPC. TIN has also been added to the Adverse events section, based on a review of the cumulative post-marketing cases associated with the use of daptomycin. The Package Leaflet is updated accordingly. In addition, QRD-related, spelling, formatting and spacing corrections were implemented.	16/07/2020	29/01/2021	SmPC and PL	As part of routine pharmacovigilance activities, the MAH identified a potential signal for tubulointerstitial nephritis (TIN) based on a review of cumulative post-marketing data. The MAH's global safety database and the EudraVigilance Data Analysis System (EVDAS) database were queried to identify all post-marketing reports with a MedDRA preferred term (PT) of tubulointerstitial nephritis, allergic nephritis, nephritis, and drug reaction with eosinophilia and systemic symptoms from IBD (12-SEP-2003) to 11-SEP-2019. A search for the PT of 'drug reaction with eosinophilia and systemic symptoms' (DRESS) was also performed. All

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				published clinical literature about daptomycin and DRESS and/or TIN was reviewed for consistency. The conclusion from the review was that there was sufficient evidence to suggest a plausible causal association of TIN to daptomycin exposure. In addition, the published cases of DRESS with end organ dysfunction, including renal impairment, were supportive of a plausible causal association to daptomycin exposure. Therefore, the findings in the MAH's safety database and the review of literature support the changes to the product information. SmPC sections 4.4 and 4.8 and PL sections 2 and 4 were amended to include text to warn prescribers and patients on TIN and DRESS when using Cubicin. For more information, please refer to the Summary of Product Characteristics.
II/0074	Submission of an updated RMP version 12.0 in order to delete all risks and additional risk minimisation measures, in line with GVP module V revision 2. Annex II of the Product Information is updated accordingly. In addition, the MAH took the opportunity to align the Product Information with the QRD template version 10.1 and update the list of local representatives. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	13/02/2020	29/01/2021	Annex II, Labelling and PL	According to guidelines given in GVP module V revision 2, it was is agreed that the safety concerns could be deleted from the RMP. It was concluded that the additional risk minimisation measures (Dosing guide and the Laboratory susceptibility testing leaflet) are no longer needed. Accordingly, the requirement concerning these two guiding documents were deleted from Annex II

	where significant assessment is required				
IB/0073	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/10/2019	n/a		
PSUSA/931/201809	Periodic Safety Update EU Single assessment - daptomycin	11/04/2019	n/a		PRAC Recommendation - maintenance
IA/0072/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	02/04/2019	n/a		
IA/0071/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	14/12/2018	14/11/2019	Annex II and PL	
T/0069	Transfer of Marketing Authorisation	17/07/2018	08/08/2018	SmPC, Labelling and PL	
PSUSA/931/201709	Periodic Safety Update EU Single assessment - daptomycin	26/04/2018	25/06/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/931/201709.

IAIN/0068	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	12/02/2018	n/a		
II/0066	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/01/2018	25/06/2018	SmPC	
II/0061	Extension of indication to extend the S. aureus bacteraemia indication to include paediatric patients 1 to 17 years of age; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated accordingly. In addition, the marketing authorisation holder (MAH) took the opportunity to bring the product information in line with the latest QRD template version 10 and to combine the SmPCs for both strengths (350 and 500 mg). The MAH also updated the RMP, from last approved version 9.1 to the current version 10.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	12/10/2017	16/11/2017	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion – Cubicin II-61.
IA/0065/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	01/09/2017	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation				
PSUSA/931/201609	Periodic Safety Update EU Single assessment - daptomycin	21/04/2017	16/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/931/201609.
IAIN/0064/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.7 - Administrative change - Deletion of	06/06/2017	16/11/2017	Annex II and PL	

	manufacturing sites				
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/2017	16/06/2017	Labelling	
IB/0060/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	02/02/2017	n/a		
IAIN/0062	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	13/01/2017	n/a		

	site				
IAIN/0058	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	21/07/2016	16/06/2017	Annex II and PL	
IAIN/0057	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	21/07/2016	16/06/2017	Annex II and PL	
PSUSA/931/201509	Periodic Safety Update EU Single assessment - daptomycin	28/04/2016	24/06/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/931/201509.
T/0056	Transfer of Marketing Authorisation from Novartis Europharm Ltd. to Merck Sharp & Dohme Ltd. Transfer of Marketing Authorisation	31/03/2016	25/04/2016	SmPC, Labelling and PL	
II/0053/G	This was an application for a group of variations. Extension of indication to extend the age range for the indication "complicated skin and soft-tissue infections" (cSSTI), to include paediatric patients from 1 to 17 years of age; as a consequence, sections 4.1, 4.2, 4.4, 5.1, 5.2 and 6.6 of the Cubicin SmPC are amended. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 9.1	22/10/2015	19/11/2015	SmPC and PL	As part of the clinical development programme, the Market Authorisation holder (MAH) has performed a number of post-authorisation studies in the paediatric population to support the safety, efficacy and dosing recommendations. Results from single dose, pharmacokinetic/safety studies paediatric subgroups, together with results obtained in DAP-PEDS-07-03 (a phase IV, multicentre, randomised, investigator blinded trial in 389 paediatric patients; age range: 1 to 17 years old), established that higher doses are

	has been agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				required in children (varying according to age groups), in order to produce exposures equivalent to that seen for efficacy in adults. These trials led to the selection of a well-characterised, efficacious, dosing regimen for paediatric patients with cSSSIs. Moreover, from these studies, as well as from data obtained in 81 paediatric patients included in a retrospective registry (with daptomycin for the treatment of a serious Gram-positive bacterial infection), no new adverse events of concern were identified and the safety data from these paediatric patients were consistent with the known safety profile of daptomycin. The overall benefit-risk balance of daptomycin for the treatment of cSSSI in the paediatric population (1-17 years of age) is favourable. For more information please refer to the scientific discussion Cubicin H-C-637-II-53-G.
IA/0054	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	16/11/2015	n/a		
II/0052/G	This was an application for a group of variations. C.I.4 Update of section 6.6 of EU SmPC in order to add information on Special precautions for disposal and other handling. The Package Leaflet is updated accordingly. A.1 Update of the address of the MAH (Novartis	21/05/2015	19/11/2015	SmPC, Labelling and PL	Section 6.6 of the SmPC is updated (Special precautions for disposal and other handling) to include the size of the needle to be used during reconstitution of the product as well as other additional handling information. Accordingly, the Package leaflet (Annex IIIB) is also updated for "Information intended for healthcare professionals only" under subheading "Instructions for use and handling" to reflect the proposed changes in the SmPC. The SmPC, Labelling and Package Leaflet of Cubicin are

	Europharm Ltd.), from Wimblehurst Road, Horsham West Sussex, RH12 5AB to Frimley Business Park, Camberley GU16 7SR, UK. The SmPC, Labelling and Package leaflet are updated accordingly. In addition, the list of local representatives in the PL is being revised. The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				also updated to reflect the new address of the MAH, Novartis Europharm Ltd., Frimley Business Park, Camberley GU16 7SR, UK.
II/0051	Update of sections 4.4 and 5.3 in the SmPC to reflect new safety information based on non-clinical study (DA.032TX.002) in neonatal dogs. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	19/11/2015	SmPC	
PSUSA/931/201409	Periodic Safety Update EU Single assessment - daptomycin	10/04/2015	n/a		PRAC Recommendation - maintenance
IB/0049/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any	30/09/2014	n/a		

	manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				

IB/0047	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/04/2014	09/04/2015	SmPC, Annex II and PL	
PSUV/0046	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IB/0048/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or Ph. Eur. 2.9.6 B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	08/04/2014	09/04/2015	SmPC and PL	
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/11/2013	03/12/2013	PL	
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
II/0042/G	This was an application for a group of variations.	13/12/2012	n/a		

	Changes in the manufacturing process of the active substance B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test				
IAIN/0043	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	07/12/2012	03/12/2013	Annex II and PL	

IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	17/08/2012	n/a		
IG/0148/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	22/02/2012	n/a		
II/0039	To include "angioedema" and "DRESS" as new ADRs in section 4.8 of SmPC. It is also proposed to include ADR "cough" in section 4.8 of SmPC. The footnote of the ADRs table has been updated in line with SmPC guideline Some minor editorial changes to SmPC are also proposed. The package leaflet has been amended accordingly. Some minor editorial changes to PL are also	19/01/2012	21/02/2012	SmPC, Annex II, Labelling and PL	The current approved SmPC of Cubicin already lists a number of manifestations of allergic and hypersensitivity-type reactions and infusion reactions that are highly likely to represent drug related reactions including infusion site reactions, hypersensitivity reactions, eosinophilia, rash, vesiculobullous rash with or without mucous membrane involvement, pruritus, urticaria, and anaphylaxis. However, based on the cumulative review of the cases related to hypersensitivity reaction and Severe Cutaneous

	proposed. In addition, Product Information has been updated to implement QRD template version 8. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Adverse Reactions (SCARs) received during the PSUR reporting period (12 September 2009 – 11 September 2010), angioedema and DRESS are added to SmPC. The MAH has also proposed to include 'cough' in SmPC Section 4.8 under SOC Respiratory, thoracic and mediastinal disorders, with frequency category 'unknown'. The rationale for this inclusion was based on the cumulative review by Cubist of all cases where cough was reported from launch (September 11, 2003) to May 19, 2011. Corresponding changes are made to the Package Leaflet. The benefit–risk balance of Cubicin 350mg/ 500mg powder for solution for injection or infusion remains unchanged.
IG/0088/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	11/07/2011	n/a		
IA/0036	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	27/05/2011	n/a		
II/0035	Update of Summary of Product Characteristics (SmPC) and Package Leaflet (PL).	16/12/2010	21/01/2011	SmPC, Annex II and PL	Based on emerging spontaneous and literature reports of eosinophilic pneumonia occurring in association with

	Update of SPC section 4.4 "Special warnings and precautions for use" and section 4.8 "Undesirable effects" to include eosinophilic pneumonia. The PL has been amended accordingly. In addition, the MAH updates the contact phone number for Poland and updates Annex II due to recent DDPS changes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Cubicin, the Marketing Authorisation Holder (MAH) was asked in June 2010 to address this risk. The MAH provided a response in July 2010 which proposed inclusion of eosinophilic pneumonia in sections 4.4 and 4.8 of the SPC and corresponding sections of the PL.
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of	21/12/2010	n/a		

	pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
R/0034	Renewal of the marketing authorisation.	23/09/2010	29/11/2010	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Cubicin continues to be favourable. The MAH will continue to submit a yearly PSUR.
II/0032/G	This was an application for a group of variations. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	22/07/2010	26/08/2010	SmPC, Annex II, Labelling and PL	
II/0027	Update of Summary of Product Characteristics Update of sections 4.2, 4.4 and 5.2 of the SPC further to the evaluation of Cubicin Follow-up measure (FUM) 005 to modify the dose recommendations for patients with Right-sided Infective Endocarditis or complicated Skin and Soft Tissue Infection associated with S.aureus	22/07/2010	26/08/2010	SmPC	Following the completion of FUM005 (renal study DAP-4REN-03-06 in infected patients), the closure of a new study DAP-REN-07-01 (renal study in non-infected subjects) and additional post-marketing data (CORE and EUCORE Registries), changes in the posology for patients with renal failure and with RIE or cSSTI associated with bacteraemia are accepted:

	bacteraemia and with renal insufficiency. Update of Summary of Product Characteristics				• A dosing recommendation of 6 mg/kg once daily in patients with CrCl from 30 mL/min to 49 mL/min. • A dosing recommendation of 6 mg/kg Q48hr in patients with CrCl < 30 mL/min. • A dosing recommendation of 6 mg/kg Q48hr for patients on hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD). These conclusions are based on the PK data collected in the pivotal efficacy study, in PK studies on patients with various degree of renal impairment, on an updated population PK analysis which included data from recent PK studies, and on simulations using the updated population PK analysis.
IB/0033/G	This was an application for a group of variations. To add a new pack size of five vials for both product strengths (350mg and 500mg). B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	22/07/2010	22/07/2010	SmPC, Labelling and PL	
II/0029	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number.	18/02/2010	26/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0 and product specific version 7.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS containes all required elements.

	Changes to QPPV Update of DDPS (Pharmacovigilance)				
II/0028	Update of Summary of Product Characteristics To update section 5.3 of the SPC in order to include results from studies elucidating the skeletal muscle effects of daptomycin further to the assessment of the preclinical follow-up measure FUM 001. Update of Summary of Product Characteristics	21/01/2010	15/03/2010	SmPC	On the basis of preclinical data from in vivo investigations to quantify the type and magnitude of the effect of daptomycin on different skeletal muscles and in vitro experiments designed to investigate the effects of daptomycin on membrane integrity using primary rat skeletal myotube cultures, the plasma membrane and possibly mitochondria of spontaneously contracting differentiated skeletal myofibers were identified as the targets of the toxicity of daptomycin; however the specific component expressed on the cell membrane (e.g. cell surface protein, receptor etc) that is directly targeted by daptomycin to initiate damage to the plasma membrane was not identified. Furthermore, the role, if any, of the mitochondrial toxicity in the myopathy is not understood. The SPC was updated to reflect this finding accordingly.
IB/0031	B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue	12/03/2010	n/a		
IA/0030	To change in the name of the approved quality control testing site from Tepnel Scientific Services, Ltd (Appleton Parkway, Livingston EH54 7EZ, UK) to Gen-Probe Life sciences Ltd (Appleton Place Appleton Parkway, Livingston, West Lothian EH54 7EZ, UK).	04/03/2010	n/a		

	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)				
II/0026	Update of section 6.3 to correct a typographical error related to the stability duration of the reconstituted solution in the vial and update of section 6.6 of the SPC to correct information pertaining to the reconstitution of Cubicin. The package leaflet is corrected accordingly. The terminology to describe sodium chloride has been harmonized with this standard terminology and the contact details for the Slovenian representative have been updated in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	16/07/2009	SmPC and PL	Section 6.3 and section 6.6 of the SPC have been updated to correct information pertaining to the reconstitution of Cubicin to clearly express that once Cubicin for infusion has been reconstituted with either water for injection or sodium chloride 9 mg/ml (0.9%) the reconstituted solution should only be diluted with sodium chloride 9 mg/ml (0.9%). Cubicin for injection should only be reconstituted with sodium chloride 9 mg/ml (0.9%). Other corrections have been made to section 6.3 pertaining to the stability duration of the reconstituted solution in the vial.
X/0023	Annex I_2.(d) Change or addition of a new pharmaceutical form	19/02/2009	17/04/2009	SmPC, Labelling and PL	Two pharmacokinetic studies in healthy volunteers support a change to allow for a different preparation and administration of Cubicin saline-reconstituted solution (i.e. without further dilution) as an intravenous injection over 2 minutes for the exact same 350 mg and 500 mg vials. The CHMP agreed that one pharmaceutical form name should encompass the planned addition of the option to give Cubicin as an intravenous injection over 2 minutes and the existing method of administration as an intravenous infusion. As such the pharmaceutical form name has been changed from powder for concentrate for solution for

					infusion to powder for solution for injection or infusion.
X/0022	Annex I_2.(d) Change or addition of a new pharmaceutical form	19/02/2009	17/04/2009	SmPC, Labelling and PL	Two pharmacokinetic studies in healthy volunteers support a change to allow for a different preparation and administration of Cubicin saline-reconstituted solution (i.e. without further dilution) as an intravenous injection over 2 minutes for the exact same 350 mg and 500 mg vials. The CHMP agreed that one pharmaceutical form name should encompass the planned addition of the option to give Cubicin as an intravenous injection over 2 minutes and the existing method of administration as an intravenous infusion. As such the pharmaceutical form name has been changed from powder for concentrate for solution for infusion to powder for solution for injection or infusion.
IB/0025	IB_10_Minor change in the manufacturing process of the active substance	13/03/2009	n/a		
IA/0024	IA_05_Change in the name and/or address of a manufacturer of the finished product	30/01/2009	n/a		
II/0021	Update of sections 4.4 "Special warnings and precautions for use" and 5.1 "Pharmacodynamic properties" of the SPC concerning clinical efficacy against infections due to enterococci as requested by CHMP in December 2007. Update of Summary of Product Characteristics	30/05/2008	22/07/2008	SmPC	EMEA has identified a signal via Eudravigilance regarding clinical failures that have occurred with Cubicin in the treatment of enterococcal infections, mostly accompanied by bacteraemia. All reported cases were from the United States. Daptomycin has been used by physicians in the US to treat enterococcal bloodstream infections including endocarditis, particularly in the setting of vancomycin resistant enterococci. Treatment of enterococcal infections, including those associated with bacteraemia, is not a licensed indication for Cubicin in the EU since an appropriate dosage schedule for treating enterococcal infections, with or without

					bacteraemia, has not been identified. However, when faced with vancomycin-resistant enterococci and/or patients with few treatment options for their enterococcal infections for various reasons it seems inevitable that physicians in the EU could consider "off-label" use of daptomycin. Therefore, the SPC was revised to strengthen the warnings and statements to make prescribers aware that failures with daptomycin in the treatment of enterococcal infections that were mostly accompanied by bacteraemia have been reported. Furthermore, in some instances treatment failure has been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin.
II/0015	Change(s) to the test method(s) and/or specifications for the active substance	24/04/2008	29/04/2008		
IA/0020	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	12/03/2008	n/a		
IA/0019	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/03/2008	n/a		
IA/0017	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/03/2008	n/a		
IA/0016	IA_13_a_Change in test proc. for active substance - minor change	17/01/2008	n/a		
II/0011	Update of Summary of Product Characteristics. To update sections 4.4, 4.5 and 4.8 of the SPC upon CHMP request following evaluation of PSUR 2	15/11/2007	19/12/2007	SmPC	Renal insufficiency was further characterised to include renal impairment and renal failure to describe the finding from clinical trials. This change was reflected in section 4.4 and 4.8 of the SPC. Following post-marketing reports

	(covering the period from 12.03.06 to 11.09.06) and 3 (covering the period from 12.09.2006 to 11.03.2007) to include post-marketing information on renal insufficiency, peripheral neuropathy and interference with particular reagents used in some assays of PI/INR. Furthermore, the MAH took the opportunity of this variation to introduce minor changes in the SPC. Update of Summary of Product Characteristics				"Peripheral neuropathy" was included to the post-marketing heading of section 4.8 of the SPC. Section 4.5 was revised to state that administration of daptomicyn can interfere with more than one reagent in the Protrombin Time/international Normalised ratio (PT/INR) assay.
IA/0014	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/11/2007	n/a		
IA/0013	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/11/2007	n/a		
IA/0012	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/11/2007	n/a		
II/0005	Extension of the Therapeutic indications to include treatment of right-sided infective endocarditis (RIE) due to Staphylococcus aureus and Staphylococcus aureus bacteraemia (SAB) when associated with RIE or with cSSTI. Extension of Indication	19/07/2007	31/08/2007	SmPC, Annex II and PL	Please refer to the Scientific Discussion: Cubicin-H-C-637-II-05-AR.
IB/0009	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	06/06/2007	n/a		

IB/0008	IB_17_a_Change in re-test period of the active substance	06/06/2007	n/a		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/05/2007	n/a	PL	
IA/0010	IA_13_a_Change in test proc. for active substance - minor change	04/05/2007	n/a		
IA/0007	IA_09_Deletion of manufacturing site	04/05/2007	n/a		
II/0003	Quality changes	18/10/2006	23/10/2006		
T/0004	Transfer of Marketing Authorisation	26/06/2006	25/07/2006	SmPC, Labelling and PL	
IA/0001	IA_06_a_Change in ATC code: Medicinal products for human use	17/03/2006	n/a	SmPC, Labelling and PL	