EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doribax

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
PSUV/0025	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
II/0024	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/01/2014	n/a		This variation concerns the assessment of the results of an open-label study to evaluate the penetration of doripenem in the cerebrospinal fluid in paediatric subjects from birth to less than 1 year of age. This study was terminated early in July 2013 and only one patient was enrolled. The observed plasma concentrations of doripenem and doripenem-M-1 in this single subject were in line with previously generated

[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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

					data. No changes were made to the Product Information.
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
R/0021	Renewal of the marketing authorisation.	21/02/2013	17/04/2013		
II/0022	Update of the safety information in sections 4.4. and 4.8 of the SmPC in order to add a warning to include the risk of seizures in patients with pre-existing CNS disorders, compromised renal function and at doses higher than 500 mg and to add seizures as an adverse drug reaction. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make a minor editorial change to section 4.2 of the SmPC. Furthermore, the PI is being brought in line with the latest QRD template version 8.3. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/02/2013	17/04/2013	SmPC, Annex II, Labelling and PL	An increasing number of post-marketing cases of seizures during Doribax treatment was reported by the marketing authorisation holder, who presented data on the occurrence of seizures during and after treatment with Doribax, including an analysis concerning the occurrence of seizures in patients with pre-existing CNS disorders, renal insufficiency and those administered doses greater than 500 mg was also conducted. Based on the analysis of the above, CHMP supported the proposed update of the safety information in sections 4.4. and 4.8 of the SmPC and agreed to add a warning to include the risk of seizures in patients with pre-existing CNS disorders, compromised renal function and at doses higher than 500 mg and to add seizures as an adverse drug reaction. A minor editorial change in section 4.2 of the SmPC was also agreed upon. The product information was brought in line with the latest QRD template version 8.3.
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
A20/0019	Pursuant to Article 20 of Regulation (EC) No. 726/2004, the European Commission requested the CHMP to re-evaluate the benefit-risk balance of Doribax in light of newly available data from the early	21/06/2012	23/08/2012	SmPC, Annex II, Labelling and PL	Please refer to the assessment report: EMEA/H/C/891/A-20/0019

	terminated DORINOS-3008 study. This study was terminated early upon recommendation of the Independent Data Monitoring Committee (IDMC), as it showed inferior efficacy and higher mortality of Doribax in relation to the control. The DORINOS-3008 study was conducted in the approved indication of ventilator-associated pneumonia, but with a different dosage regimen (1g infused over 4 hours, every 8 hours, for 7 days) than that currently approved. In light of the above, the European Commission requested the CHMP to assess the results of DORINOS-3008 and their impact on the benefit-risk balance of Doribax, and give its opinion on whether the marketing authorisation should be maintained, varied, suspended or withdrawn.				
II/0015	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet To update sections 4.2, 4.4, 4.9 and 5.2 of the SmPC to include dosing recommendations for patients on continuous renal replacement therapies (CRRT) based on a single-dose PK study of doripenem 500 mg iv in dialysis-dependent subjects with stage 5 chronic kidney disease and a pharmacometric analysis from this study. The MAH took also the opportunity to amend the level of renal impairment in section 4.2 in line with the CHMP Note for Guidance on the evaluation of the pharmacokinetics of medicinal products in patiens with impaired renal function, to include further minor corrections throughout the SmPC, Labelling and PL, to update Annex II in line with the CHMP	19/05/2011	01/08/2011	SmPC, Annex II, Labelling and PL	Based on simulations using data from a conventional pharmacokinetic study assessed in FUM 008, the MAH proposed a dosing regimen in patients receiving continuous renal replacement therapy (CRRT), such as continuous venovenous haemofiltration (CVVH) with a glomerular filtration rate ? 30 ml/min and continuous venovenous haemodiafiltration (CVVHDF) with glomerular filtration rate < 5 ml/min, as well as 5-30 ml/min. The simulations indicate that the patients will reach a > 90% probability of target attainment (>35% T>MIC) for pathogens with MIC? 1 mg/l. Pathogens with a higher MIC are not sufficiently covered, however increasing the dose would lead to further increased exposure of the doripenem-M-1 metabolite, which should be avoided. Furthermore, already with the proposed dose regimen, the exposure of the metabolite may be increased as the estimations of the metabolite exposure may not be

	recommendations concerning the DDPS version number and to update the list of local representatives in the PL. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				completely accurate. There are no indications that the metabolite would be pharmacologically active. However, the "off-target" pharmacological activity has not been investigated and thus the clinical consequences are unknown. The Product Information was updated to reflect these findings.
IG/0090/G	This was an application for a group of variations. 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.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	08/07/2011	n/a		
II/0016	Update of section 5.2 of the Summary of Product Characteristics to include pharmacokinetic information for adult patients with cystic fibrosis. The MAH took the opportunity to correct the existing information in section 5.2 of the Summary of Product Characteristics regarding the gender effect on the pharmacokinetics. The MAH also deleted the reference to the version and date of the detailed description of the pharmacovigilance system (DDPS) from Annex II B, following the October 2010 CHMP guidance on the issue.	14/04/2011	14/06/2011	SmPC and Annex II	Following the submission of the results of a pharmacokinetic study (DORI-NOS-1009) which intended to characterise the PK of doripenem and its metabolite (doripenem-M-1) after a single 1 g and a single 2 g doripenem 4-hour i.v. infusion administered to adult subjects with cystic fibrosis in stable condition and not requiring hospitalisation and to further explore the safety and tolerability of Doribax, the MAH submitted this variation to update section 5.2 to include the pharmacokinetic information for adult patients with cystic fibrosis. The MAH used the opportunity to also correct the existing information on the gender effect on the pharmacokinetics and to revise Annex II B by deleting the

	The MAH took the opportunity to update the version number and date of the Risk Management Plan in Annex II B, as decided by the CHMP in February 2011. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				reference to the version and date of the DDPS and by updating the version number and date of the Risk Management Plan.
II/0014	Update of sections 4.9 and 5.2 of the SmPC to reflect information from 2 new Phase 1 Clinical Studies. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	03/11/2010	SmPC	Following the assessment of FUM 7 concerning Phase 1 study CSR DORI-NOS-1011 the CHMP requested in a RSI the results from a similar study performed by Shionogi and Co. Ltd. To fulfil FUM 7 and in response to the above RSI, the MAH submitted in this application the final study report of the requested study DORI-R141A. In addition the MAH requested an update to Sections 4.9 and 5.2 of the SmPC to add information on rash and pharmacokinetics respectively, based on the results of both studies (DORI-NOS-1011 and DORI-R141A). The proposed changes were endorsed by the CHMP with a minor amendment considered necessary to provide adequate information to the prescriber.
IG/0023/G	This was an application for a group of variations. 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 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	21/09/2010	n/a	Annex II	

IB/0013	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/07/2010	n/a	SmPC, Annex II, Labelling and PL	
IA/0012	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	04/06/2010	n/a	Annex II	
II/0011	Update of section 4.8 of the SmPC to include the term thrombocytopenia and to update the term neutropenia following CHMP assessment of the second PSUR (12 October 2008 to 11 April 2009). Section 4 of the PL was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives of Greece, and to update the details of the European Medicines Agency and to amend changes introduced with variation II-10 in Annex II in agreement with QRD template. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	27/04/2010	SmPC and PL	A cumulative review of phase III clinical studies, review of biological plausibility and pharmacological class effect, epidemiology of thrombocytopenia, and post-marketing cases, was performed following the review of the 2nd Periodic Safety Updated Report for Doribax. The review showed that thrombocytopenia as defined by platelet count less than 100,000/mm3 was considered an adverse drug reaction associated with the use of doripenem. Key factors supporting this conclusion include 2 cases with positive dechallenge with reporting frequency uncommon. The term neutropenia has been also updated after review of post-marketing data to show that this adverse drug reaction has an uncommon frequency.
II/0010	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to version 5 to include non-QPPV related changes. Consequently, Annex II has been updated with the new version number of the DDPS. Update of DDPS (Pharmacovigilance)	18/02/2010	27/04/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (version 5) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.
X/0009	Addition of a new strength 250 mg powder for solution for infusion	17/12/2009	15/03/2010	SmPC, Labelling and PL	

	X-3-iii_Addition of new strength				
II/0005	Update of section 4.8 of the SPC following the assessment of the PSUR covering the period 11/08/2007-11/10/2008 to include the terms Toxic Epidermal Necrolysis (TENs) and Stevens-Johnson syndrome (SJS). The PL has been updated accordingly. The MAH took the opportunity to amend the contact details of local representative in Bulgaria. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	17/09/2009	SmPC and PL	Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare, life-threatening cutaneous adverse reactions. The etiology of SJS and TEN is usually drug-related with more than 100 drugs that have been implicated as the cause in case reports and studies. Further to the assessment of the first PSUR for doripenem in February 2009, the CHMP asked the MAH to amend the Product Information to include TEN and SJS on the basis of the following conclusion: Cumulative review of TEN/SJS included 7 cases. All cases reported confounding factors, most specifically the concomitant use of other antimicrobials. In making assessments of these severe skin reactions, it must be remembered that most antibiotics are given in combination, most especially, to patients ill enough to require treatment with doripenem. Therefore, the case for causality will always be a difficult one. At least 3 cases, while complicated with co-suspect medications, suggest temporal relationships and a positive dechallenge for doripenem and negative dechallenge for the co-suspect medication. TEN and SJS have here been added under Skin and subcutaneous tissue disorders with an unknown frequency as frequency can not be estimated from the current available data. Additionally, "Serious skin reactions, with a widespread rash with peeling skin and blisters in the mouth, eyes and genitals (toxic epidermal necrolysis or Stevens-Johnson syndrome)." has been added in section 4 of the PL.
IB/0008	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	05/08/2009	n/a	SmPC	
II/0003	Update of sections 4.4 and 4.5 of the Summary of	29/05/2009	14/07/2009	SmPC and PL	To support this Type II variation II/03, the MAH submited the

	Products Characteristics (SPC) to add the interaction between doripenem and valproic acid as a result of a drug-drug interaction study in healthy human volunteers. The Package Leaflet (PL) has been updated accordingly. The MAH also took the opportunity to make some minor corrections to the SPC and PL. Update of Summary of Product Characteristics and Package Leaflet				result of an open-label, single-sequence, drug-drug interaction study of i.v. doripenem co-administered with oral VPA planned in 24 healthy subjects. Based on the results, the MAH proposed a change to section 4.5 that CHMP disagreed with due to the large interaction seen and contra-proposed the inclusion of a warning to section 4.4 of the SPC to indicate that the concomitant use of doripenem and valproic acid/sodium valproate is not recommended. More information have also been added in section 4.5 of the SPC.
IA/0007	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	10/07/2009	n/a		
IA/0006	IA_05_Change in the name and/or address of a manufacturer of the finished product	26/06/2009	n/a		
IB/0004	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	30/04/2009	n/a		
II/0002	Quality changes	19/03/2009	24/03/2009		
IB/0001	IB_30_b_Change in supplier of packaging components - replacement/addition	05/09/2008	n/a		