EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for Doribax

Review under Article 20 of **Regulation (EC) No 726/2004**, as amended

INN: Doripenem

Procedure number: EMEA/H/C/891/A-20/0019

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

In December 2011, the Marketing Authorisation Holder (MAH) for Doribax submitted preliminary results of study DORINOS3008, which 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 DORINOS3008 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 on 20 January 2012 to assess the results of DORINOS3008 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of Doribax, and give its opinion on whether the marketing authorisation should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

Carbapenems as broad spectrum antibacterial agents are often used as empiric therapy since they provide coverage against both gram positive and gram negative pathogens. Multiple studies have shown that patients with severe infections, if treated early with agents that are effective against infecting organisms, have better survival rate than those treated initially with agents of suboptimal antibacterial activity.

Nosocomial pneumonia (NP) is the second most common hospital-acquired infection, with ventilator-associated pneumonia (VAP) being the most common intensive care unit-acquired infection. It is caused by a broad range of bacteria, and is associated with a high risk of morbidity, especially in mechanically-ventilated patients. Because the mortality rate and other complications from NP can be high, effective management of these infections requires early diagnosis and treatment with an optimal antibacterial agent with a spectrum of activity that covers a number of pathogens.

2.1. Clinical aspects

2.1.1. Clinical efficacy

The currently approved posology for Doribax in patients with nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), is 500 mg infused over 1 or 4 hours, every 8 hours (q8h). The usual treatment duration of doripenem therapy is 5-14 days and should be guided by the severity, site of the infection and the patient's clinical response.

DORI-09 and DORI-10

The initial approval of this indication was based on the dosage regimen used in the phase III studies DORI-09 and DORI-10. In both studies, doripenem was shown to be non-inferior to the comparators (piperacilin/tazobactam and imipenem, respectively). Clinical cure at the test-of-cure (TOC) visit in the clinical modified ITT populations were: DORI-09, 69.5% vs. 64.1% [95% CI -4.1; 14.8] and DORI-10, 59.0% vs. 57.8 [95% CI -7.9; 10.3]. The results were consistent for secondary endpoints. The clinical cure rates by different subgroups and the microbiological outcome per pathogen were generally consistent between the study drugs within each study. In the DORI-10 study, which only enrolled VAP patients, the 28-day all-cause mortality was 10.8% in the doripenem arm and 9.5% in the imipenem arm (95% CI: -4.4; 7.0). The pre-specified lower non-inferiority margin was set to -20% in both

studies. The average duration of therapy in DORI-10 was 8.6 days for subjects in the doripenem arm and 9.0 days for subjects in the imipenem arm.

DORINOS3008

PK/PD data in the original application of Doribax indicated that 1g infused over 4 hours q8h could further enhance the efficacy for pathogens with decreased susceptibility, although clinical efficacy and safety data for this regimen was lacking. Based on this, the study DORINOS3008 was designed: a prospective, randomised, double-blind, double-dummy, multicentre study to assess the safety and efficacy of doripenem compared with imipenem-cilastatin in the treatment of subjects with ventilator-associated pneumonia. The primary objective of the study was to demonstrate that a 7-day course of doripenem at 1g infused over 4 hours q8h was non-inferior to a 10-day course of imipenem-cilastatin at 1g infused over 1 hour q8h. This study was terminated early by the MAH following a recommendation of the IDMC, who reviewed data from 49% of the total number of patients targeted for enrolment. The IDMC considered that the data showed signs of inferior efficacy and higher mortality of doripenem compared to imipenem. The signals were close to the pre-specified stopping limits. Five (5) sites that enrolled a total of 41 patients were deemed to be GCP non-compliant prior to database lock and excluded from the primary analyses of efficacy and safety.

During this study, the 233 patients were allowed to receive specified adjunctive therapies. The clinical cure rate at the end of treatment visit on day 10 was numerically lower for subjects in the doripenem arm of the primary microbiological intent-to-treat (MITT) (45.6% vs. 56.8%; 95% CI: -26.3%; 3.8%) and co-primary microbiologically evaluable (ME) (49.1% [28/57] vs. 66.1% [39/59]; 95% CI: -34.7%; 0.8%) analysis sets. The overall 28-day all-cause mortality rate was numerically higher for doripenem treated subjects in the MITT analysis set (21.5% vs. 14.8%; 95% CI: -5.0%; 18.5%).

The study was prematurely stopped and thus the number of subjects in both treatment arms was small (MITT population N=79 (doripenem) and N=88 (imipenem), respectively) and the results are difficult to interpret, as it lacks statistical power to draw adequate conclusions.

Table 1 Failures at EOT by treatment duration and subgroups - excluding 5 sites (study DORINOS3008: microbiologically intent-to-treat analysis set)

		--------- Doripenem --------		--------- Imipenem ---------	
Parameter	Value	≤ 7 Days	>7 Days	≤ 7 Days	>7 Days
Overall	All Subjects	12/43 (27.9%)	31/43 (72.1%)	12/38 (31.6%)	26/38 (68.4%)
Pathogen Classification	*P.Aeruginosa*	2/10 (20.0%)	8/10 (80.0%)	1/4 (25.0%)	3/4 (75.0%)
	Acinetobacter Spp.	3/9 (33.3%)	6/9 (66.7%)	1/5 (20.0%)	4/5 (80.0%)
	Enterobacteriaceae	4/20 (20.0%)	16/20 (80.0%)	5/20 (25.0%)	15/20 (75.0%)
	Sp. Gram Neg Pathogens(a)	9/33 (27.3%)	24/33 (72.7%)	7/28 (25.0%)	21/28 (75.0%)
	All Gram Neg Pathogens	9/38 (23.7%)	29/38 (76.3%)	10/34 (29.4%)	24/34 (70.6%)
	All Gram Pos Pathogens	4/13 (30.8%)	9/13 (69.2%)	4/15 (26.7%)	11/15 (73.3%)
APACHE II Score	≤ 15	3/14 (21.4%)	11/14 (78.6%)	2/15 (13.3%)	13/15 (86.7%)
	16-19	3/16 (18.8%)	13/16 (81.3%)	5/11 (45.5%)	6/11 (54.5%)
	≥ 20	6/13 (46.2%)	7/13 (53.8%)	5/12 (41.7%)	7/12 (58.3%)
CPIS	<6	0/2	2/2 (100%)		
	6-7	9/24 (37.5%)	15/24 (62.5%)	8/26 (30.8%)	18/26 (69.2%)
	8-9	2/11 (18.2%)	9/11 (81.8%)	3/9 (33.3%)	6/9 (66.7%)
	>9	1/5 (20.0%)	4/5 (80.0%)	1/3 (33.3%)	2/3 (66.7%)
	Missing	0/1	1/1 (100%)		
Creatinine Clearance	<150 ml/min	9/33 (27.3%)	24/33 (72.7%)	10/30 (33.3%)	20/30 (66.7%)
	≥ 150 ml/min	3/10 (30.0%)	7/10 (70.0%)	2/8 (25.0%)	6/8 (75.0%)
Dose Adjusted	No	5/23 (21.7%)	18/23 (78.3%)	7/22 (31.8%)	15/22 (68.2%)
	Yes	7/20 (35.0%)	13/20 (65.0%)	5/16 (31.3%)	11/16 (68.8%)
PaO2/FiO2	≤ 250	8/30 (26.7%)	22/30 (73.3%)	7/23 (30.4%)	16/23 (69.6%)
	>250	4/13 (30.8%)	9/13 (69.2%)	5/15 (33.3%)	10/15 (66.7%)
Bacteremia	No	9/38 (23.7%)	29/38 (76.3%)	12/37 (32.4%)	25/37 (67.6%)
	Yes	3/5 (60.0%)	2/5 (40.0%)	0/1	1/1 (100%)
Adjunctive Therapy	No	3/24 (12.5%)	21/24 (87.5%)	9/26 (34.6%)	17/26 (65.4%)
	Yes	9/19 (47.4%)	10/19 (52.6%)	3/12 (25.0%)	9/12 (75.0%)
	≤ 72 Hrs	8/16 (50.0%)	8/16 (50.0%)	3/9 (33.3%)	6/9 (66.7%)
	>72 Hrs	1/3 (33.3%)	2/3 (66.7%)	0/3	3/3 (100%)
Adjunctive Aminoglycoside	No	5/11 (45.5%)	6/11 (54.5%)	2/6 (33.3%)	4/6 (66.7%)
	Yes	4/8 (50.0%)	4/8 (50.0%)	1/6 (16.7%)	5/6 (83.3%)
	≤ 72 Hrs	4/8 (50.0%)	4/8 (50.0%)	1/6 (16.7%)	5/6 (83.3%)
Adjunctive Vancomycin/Linezolid	No	0/3	3/3 (100%)	1/3 (33.3%)	2/3 (66.7%)
	Yes	9/16 (56.3%)	7/16 (43.8%)	2/9 (22.2%)	7/9 (77.8%)
	≤ 72 Hrs	9/14 (64.3%)	5/14 (35.7%)	2/7 (28.6%)	5/7 (71.4%)
	>72 Hrs	0/2	2/2 (100%)	0/2	2/2 (100%)
Investigator Outcome	Missing	3/5 (60.0%)	2/5 (40.0%)	0/3	3/3 (100%)
	Cure	0/1	1/1 (100%)	1/3 (33.3%)	2/3 (66.7%)
	Failure	3/18 (16.7%)	15/18 (83.3%)	3/14 (21.4%)	11/14 (78.6%)
	Indeterminate	6/19 (31.6%)	13/19 (68.4%)	8/18 (44.4%)	10/18 (55.6%)

(a) *Pseudomonas Aeruginosa, Acinetobacter,* or *Enterobacteriaceae*

The study DORINOS3008 included a population representative of seriously ill patients. In spite of differences in study design between the pivotal studies and DORINOS3008, there are several similarities, especially between DORI-10 and DORINOS3008. All subjects in DORI-10 and DORINOS3008 had VAP. The severity of illness in DORI-10 was similar to the severity of illness in DORINOS3008. The majority of subjects in these studies had APACHE II scores of ≥16 and over 25% of the subjects had APACHE II scores ≥20. Over 30% of subjects had CPIS >7.

Most subjects in both treatment groups were assessed as clinical failures after day 7. A similar number of patients in each group failed up to day 7, while a relatively higher number of patients in the doripenem group failed after day 7.

Higher 28-day all-cause mortality rates were seen for subjects in the doripenem arm for most baseline characteristics assessed and no single characteristic is considered to explain the difference in 28-day all-cause mortality rates between treatment groups. While mortality rates for subjects with APACHE Scores ≤15 were similar between treatment groups for all analysed study populations, higher mortality rates were seen in subjects in the doripenem treatment arm with APACHE scores of 16-19 and ≥20 compared to the imipenem arm.

Several factors may have contributed to the low clinical response among doripenem treated patients. There were some imbalances in baseline characteristics between study groups in favour for the imipenem group, which may have partly contributed to the study results, considering the small number of evaluable patients. A larger proportion of subjects in the doripenem treatment arm had an APACHE II score >15 (57.0% doripenem, 52.3% imipenem); PaO2/FiO2 ≤250 (63.3% doripenem, 58.0% imipenem), and bacteraemia (7.6% doripenem, 4.5% imipenem). A larger proportion of subjects in the doripenem arm had moderate and severe renal impairment (8.8% doripenem, 5.7% imipenem) whereas a larger proportion in the imipenem arm had creatinine clearance ≥80 µg/mL. Furthermore a greater proportion of subjects in the doripenem arm of DORINOS3008 were infected with Pseudomonas aeruginosa (21.5%) compared to the imipenem arm (11.4%) and also compared to DORI-10 (14.6% doripenem, 12.8% imipenem). In addition there were higher rates of Acinetobacter in DORINOS3008 (19.0% doripenem, 11.4% imipenem) as compared to DORI-10 (8.3% doripenem, 7.9% imipenem). A higher proportion of patients in the doripenem group needed dose adjustment, which may be indicative of a more severely ill population. However, it cannot be excluded that dose adjustment within the study was suboptimal leading to an underexposure. A higher number of patients in the doripenem group compared to the imipenem group received any amount of adjunctive antibiotic therapy (doripenem 33%-38%, imipenem 23% to 32%).

The difference in clinical cure rate between doripenem and comparator was greater in patients with baseline creatinine clearance (CrCl) >150 ml/min (44.4% [8/18] vs. 71.4% [20/28]; difference -27.0%, 95%CI -55.4%; 1.4%) compared to patients with CrCl <150 ml/min (45.9% [28/61] vs. 50.0% [30/60]; difference -4.1%, 95%CI -21.9%; 13.7%). While the number of patients with augmented renal function in DORINOS3008 is very low to draw conclusions, a new PK/PD model based exclusively on VAP patients later confirmed that the 500 mg dose may be low in certain subgroups of patients, in particular those with increased renal clearance combined with infecting pathogens with high MIC values.

However, it is likely that the major contributing factor to the higher failure rate in the doripenem treated patients in DORINOS3008 was the pre-specified fixed treatment duration of 7 days for doripenem. Data from studies DORI-09 and DORI-10 indicate consistently that successful treatment of severe cases of VAP, in particular those infected with Pseudomonas aeruginosa and Acinetobacter, requires treatment duration of at least 10 days, in many cases even longer. In terms of Enterobacteriaceae, data indicates that 10 days would commonly be sufficient, thus the duration of treatment needed for these pathogens seems to be in line with that of gram-positives.

The Scientific Advisory Group (SAG) on anti-infectives was consulted and the majority of the members agreed that, although the results of this study represent a signal in this indication, the totality of the data in the NP/VAP indication is still indicative of a positive benefit-risk balance. The SAG also considered that although the short fixed duration of therapy in DORINOS3008 was an important reason behind the results of the study, it was not the only one. Other factors such as the high antibiotic clearance in a severely ill patient population may have led to suboptimal PK/PD target attainment in

some patients, and the possible emergence of resistance mainly for gram negative non-fermenters may also have played a role. The SAG also recommended that further PK/PD analyses be conducted so that a revised PK/PD model could be supported, and eventually used to determine whether a higher dose could be of benefit to patients.

2.1.2. Clinical safety

Most treatment-emergent adverse events (TEAEs) ending with death were reported for a single subject only. The most frequently reported serious TEAEs were within the system organ class of infections and infestations and respiratory, thoracic and mediastinal disorders. The only serious TEAE reported at >2% higher rate in the doripenem arm than in the imipenem arm was renal failure. The incidence of discontinuations due to TEAEs (6.1%doripenem, 6.3% imipenem) and due to study related TEAEs (0.9% in both groups) were similar in the two groups.

Table 2 Treatment-emergent serious adverse events reported by >1% subjects in either treatment arm by System Organ Class and Preferred Term - ITT analysis set - excluding 5 sites

Body System Or Organ Class Dictionary-Derived Term	Doripenem (N=115) n (%)	Imipenem (N=112) n (%)	Total (N=227) n (%)
Total no. subjects with SAE	54 (47.0)	42 (37.5)	96 (42.3)
Cardiac Disorders	9 (7.8)	9 (8.0)	18 (7.9)
Cardiac Arrest	3 (2.6)	6 (5.4)	9 (4.0)
Cardiac Failure	2 (1.7)	3 (2.7)	5 (2.2)
Gastrointestinal Disorders	5 (4.3)	5 (4.5)	10 (4.4)
General Disorders and Administration Site Conditions	4 (3.5)	4 (3.6)	8 (3.5)
Multi-organ Failure	2 (1.7)	3 (2.7)	5 (2.2)
Treatment Failure	2 (1.7)	0	2 (0.9)
Infections and Infestations	24 (20.9)	21 (18.8)	45 (19.8)
Bacteraemia	1 (0.9)	2 (1.8)	3 (1.3)
Device Related Sepsis	3 (2.6)	2 (1.8)	5 (2.2)
Empyema	2 (1.7)	0	2 (0.9)
Infections and Infestations continued			
Mediastinitis	0	2 (1.8)	2 (0.9)
Pneumonia	4 (3.5)	3 (2.7)	7 (3.1)
Sepsis	5 (4.3)	3 (2.7)	8 (3.5)
Septic Shock	6 (5.2)	6 (5.4)	12 (5.3)
Urinary Tract Infection	3 (2.6)	1 (0.9)	4 (1.8)
Injury, Poisoning and Procedural Complications	5 (4.3)	3 (2.7)	8 (3.5)
Traumatic Brain Injury	2 (1.7)	0	2 (0.9)
Nervous System Disorders	7 (6.1)	7 (6.3)	14 (6.2)
Brain Oedema	3 (2.6)	4 (3.6)	7 (3.1)
Intracranial Pressure Increased	2 (1.7)	1 (0.9)	3 (1.3)
Renal and Urinary Disorders	7 (6.1)	4 (3.6)	11 (4.8)
Renal Failure	4 (3.5)	1 (0.9)	5 (2.2)
Renal Failure Acute	2 (1.7)	2 (1.8)	4 (1.8)
Respiratory, Thoracic and Mediastinal Disorders	11 (9.6)	15 (13.4)	26 (11.5)
Acute Respiratory Distress Syndrome	2 (1.7)	1 (0.9)	3 (1.3)
Acute Respiratory Failure	1 (0.9)	2 (1.8)	3 (1.3)
Hypoxia	0	4 (3.6)	4 (1.8)
Pulmonary Embolism	1 (0.9)	3 (2.7)	4 (1.8)
Respiratory Failure	3 (2.6)	1 (0.9)	4 (1.8)
Vascular Disorders	4 (3.5)	6 (5.4)	10 (4.4)
Hypotension	0	3 (2.7)	3 (1.3)
Shock	1 (0.9)	2 (1.8)	3 (1.3)

A total of 514 patients participating in phase I, II and III studies have been exposed to doripenem 1g intravenous. Systematic analysis of the safety data from these studies did not identify new adverse reactions associated with the 1g dose of doripenem. In addition, no clinically significant differences in the safety profile of the 1g dose compared to the 500 mg dose were found. Seizures, haemolytic anaemia, renal impairment/failure and hepatic injury are adverse events of special interest for doripenem, but were found to occur within the range of that observed with the comparator groups.

2.2. Product information

The CHMP recommended the following amendments to be introduced in the summary of product characteristics (SPC):

Summary of Product Characteristics

4.2 Posology and method of administration

Posology

The recommended dose and administration by infection is shown in the following table:

Infection	Dose	Frequency	Infusion time
Nosocomial pneumonia including ventilator–associated pneumonia	500 mg or 1 g*	every 8 hours	1 or 4 hours**
Complicated intra-abdominal infection	500 mg	every 8 hours	1 hour
Complicated UTI, including pyelonephritis	500 mg	every 8 hours	1 hour

* 1 g every 8 hours as a 4-hour infusion may be considered in patients with augmented renal clearance (particularly those with creatinine clearance (CrCl) ≥150 ml/min) and/or in infections due to non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.). This dose regimen is based on PK/PD data (see sections 4.4, 4.8 and 5.1).

** Based mainly on PK/PD considerations, a 4-hour infusion time may be more suitable for infection with less susceptible pathogens (see section 5.1). This dosing regimen should also be considered in particularly severe infections.
For infusion solution shelf life see section 6.3.

The usual treatment duration of doripenem therapy ranges from 5-14 days and should be guided by the severity, site of the infection, infecting pathogen and the patient's clinical response. The usual treatment duration for patients with nosocomial pneumonia, including ventilator-associated pneumonia is 10 to 14 days and is often in the upper range for patients infected with non-fermenting gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.) (see section 5.1).

[…]

In patients with moderate renal impairment (CrCl ≥ 30 to ≤ 50 ml/min), the dose of Doribax should be 250 mg every 8 hours (see section 6.6). In patients with severe renal impairment (CrCl < 30 ml/min), the dose of Doribax should be 250 mg every 12 hours (see section 6.6). In patients receiving 1 g every 8 hours as a 4-hour infusion, the dose should be similarly adjusted (moderate renal impairment: 500 mg every 8 hours; severe renal impairment: 500 mg every 12 hours).

[…]

4.4 Special warnings and precautions for use

[…]

The selection of doripenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

Caution on the choice of antibiotic agent and dose should be taken when treating patients with late-onset ventilator-associated pneumonia (>5 days hospitalisation) and in other nosocomial

pneumonia cases where pathogens with decreased susceptibility are suspected or confirmed, such as *Pseudomonas* spp. and *Acinetobacter* spp. (see sections 4.2 and 5.1).

Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications (see section 4.1).
[…]

4.8 Undesirable effects

[…]

The safety profile in approximately 500 patients who received Doribax 1 g every 8 hours as a 4-hour infusion in phase I, II and III clinical trials, was consistent with the safety profile for patients receiving 500 mg every 8 hours.

[…]

5.1 Pharmacodynamic properties

[…]
Data from clinical studies

Ventilator-associated pneumonia

A study of 233 patients with late-onset VAP failed to demonstrate the non-inferiority of an investigational 7-day course of doripenem (1 g every 8 hours as a 4 hour infusion) compared to a 10-day course of imipenem/cilastatin (1 g every 8 hours as a 1 hour infusion). In addition, the patients were allowed to receive specified adjunctive therapies. The study was stopped early based on the recommendation of an independent data monitoring committee. The clinical cure rate at the end of treatment visit on day 10 was numerically lower for subjects in the doripenem arm of the primary microbiological intent-to-treat (MITT) (45.6% versus 56.8%; 95% CI: -26.3%; 3.8%) and co-primary microbiologically evaluable (ME) (49.1% [28/57] versus 66.1% [39/59]); 95% CI -34.7%; 0.8%) analysis sets. The overall 28-day all cause mortality rate was numerically higher for doripenem treated subjects in the MITT analysis set (21.5% versus 14.8%; 95% CI: -5.0%; 18.5%).The difference in clinical cure rate between doripenem versus imipenem/cilastatin was greater in patients with APACHE score > 15 (16/45 [36%] versus 23/46 [50%]) and in patients infected with *Pseudomonas aeruginosa* 7/17 [41%] versus 6/10 [60%]).

The corresponding amendments will also be introduced in the package leaflet, as applicable.

In addition, the product information was updated in line with the latest QRD template, so administrative changes have also been introduced to annex II and the labelling.

3. Overall conclusion and benefit/risk assessment

Based on the totality of the data available from the early terminated DORINOS3008 study, and from other relevant studies, the Committee considered that the short fixed duration of therapy with Doribax was a major contributor to the inferior outcome of the doripenem group in DORINOS3008. In addition, other factors such as imbalances at baseline between groups, in particular regarding renal function and infection with non-fermenting gram negative pathogens, may have contributed to the differences in clinical outcome and all-cause mortality between treatment groups.

The Committee therefore concluded that the recommended treatment duration in patients with nosocomial pneumonia (including ventilator-associated pneumonia) should be 10-14 days, often in the upper range for those infected with non-fermenting gram-negative pathogens.

The Committee is also of the opinion that a Doribax dose of 1g every 8 hours infused over 4 hours may need to be considered when treating patients with nosocomial pneumonia (including ventilator-associated pneumonia), particularly those with augmented renal function and/or infections with non-fermenting gram negative pathogens. Safety data from a total of 514 patients given the 1g dose in clinical trials indicates that the safety profile of this dose is comparable to that of the 500 mg dose.

The Committee has agreed also to ask the MAH to liaise with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to consider the need to revise the breakpoints for Doripenem.

The Committee, as a consequence, concluded that the benefit-risk balance of Doribax in the treatment of nosocomial pneumonia (including ventilator-associated pneumonia) remains positive under normal conditions of use, subject to the changes to the product information agreed.

The CHMP recommended the variation to the terms of the marketing authorisation for Doribax for which the revised is set out in annexes I, II, IIIA and IIIB of the opinion. The scientific conclusions and the grounds for the variation of the marketing authorisation are set out in Annex II of the opinion.

4. Action plan

4.1. Direct Healthcare Professional Communication

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate the new recommendations on dosing, duration and precautions for treatment of patients with nosocomial pneumonia with Doribax.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent by 11 July 2012.

5. Conclusion and grounds for the recommendation

Whereas,

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Doribax initiated by the European Commission.
- The Committee reviewed all available data from the DORINOS3008 study, and from other relevant studies.
- The Committee considered that the short fixed duration of therapy with Doribax was a major contributor to the inferior outcome of the doripenem group in DORINOS3008, but that other factors such as imbalances at baseline between groups, in particular regarding renal function and infection with non-fermenting gram negative pathogens, may have contributed to the differences in clinical outcome and all-cause mortality between treatment groups.
- The Committee is of the opinion that a higher Doribax dose may need to be considered in some patients, and that for nosocomial pneumonia (including ventilator-associated pneumonia) the usual duration of therapy should be clarified in the product information.

- The Committee, as a consequence, concluded that the benefit-risk balance of Doribax in the treatment of nosocomial pneumonia (including ventilator-associated pneumonia) remains positive under normal conditions of use, subject to the changes to the product information agreed.

The CHMP has therefore recommended the variation to the terms of the marketing authorisation for Doribax in accordance to the Product Information set out in annexes I, II, IIIA and IIIB.