Advice to prescribers treating patients with Doribax for nosocomial pneumonia

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Information on Doribax

Doribax is an antibiotic medicine that contains the active substance doripenem. It is used to treat adults with nosocomial pneumonia, a lung infection caught while the patient is in hospital including when the patient is being helped to breathe with a ventilator. It is also used to treat complicated infections in the abdomen and the urinary tract. Doribax has been authorised in the EU since July 2008 and is marketed in all EU Member States including Malta as a 250mg powder for infusion (drip into a vein). Dorpenem is a Carbapenem antibacterial for systemic use with ATC code J01DH04.

Information from European Medicines Agency about the safety concern

In summary:

- **A review of available data raises concerns that the currently approved dose of Doribax of 500 mg every 8 hours may not be sufficient to treat all patients with nosocomial pneumonia, including ventilator-associated pneumonia.**
- **Particular caution should be excercised in patients for whom non-fermenting gram-negative pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter* are suspected or confirmed as the cause of infection. In some of these patients doctors should consider initiating concomitant treatment with an aminoglycoside antibiotic.**
- **The benefits of Doribax continue to outweigh its risks but the CHMP has recommended updating the prescribing information to allow using a higher dose in certain patients**

In December 2011, the marketing authorisation holder for Doribax provided the European Medicines Agency with preliminary results from a clinical trial in patients with ventilator-associated pneumonia which had been terminated early on the recommendation of an independent data monitoring committee. The trial was investigating the effects of using Doribax at a higher

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dose and for a shorter treatment period than currently authorised, in severely ill patients who had been hospitalised for at least five days. Doribax was given at a dose of 1 g every eight hours for seven days (the approved dose is 500 mg every eight hours for up to 14 days). This was compared with another antibiotic medicine, imipenem-cilastatin, given at a dose of 1 g every eight hours for 10 days. A lower cure rate (45.6% vs. 56.8%) and a higher rate of death (21.5% vs. 14.8%) were seen in patients treated with Doribax compared with the comparator group.

Consequently, the European Commission asked the CHMP to assess the results of the study and their impact on the benefit-risk balance of Doribax, and give its opinion on whether the marketing authorisation for Doribax should be maintained, varied, suspended or withdrawn across the EU.

The CHMP considered the available evidence on the effectiveness and safety of Doribax in treating ventilator-associated pneumonia, including the results of the interrupted study, other studies supporting the original authorisation of Doribax in these patients, and further information requested from the company. The CHMP also consulted a group of experts in anti-infective medicines.

The CHMP decided that it was not possible to draw firm conclusions from the interrupted study. However, it concluded that the short duration of Doribax treatment was a major factor contributing to the worse results than seen with the comparator medicine, noting that better results were observed in other studies with Doribax where patients were treated for longer.

Based on the available data, the Committee considered that other factors may also influence the effectiveness of Doribax treatment in patients with hospital-acquired pneumonia. Study data indicated that treatment was less likely to succeed in critically ill patients with augmented renal clearance (where the kidneys clear the medicine from the body too quickly) and in patients whose infection involves specific types of bacteria which may require stronger antibiotic treatment. Therefore the CHMP concluded that the currently approved dose may not be enough in these situations and decided that a higher dose of 1 g Doribax every eight hours may be considered for these patients. The safety of this higher dose was confirmed by data from studies involving around 500 patients.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Doribax continue to outweigh its risks but recommended updating the prescribing information to allow using a higher dose in certain patients.

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A European Commission decision on this opinion will be issued in due course.

In Malta

For Healthcare Professionals

To inform healthcare professionals of this issue, the Medicines Authority has approved a Direct Healthcare Professional Communication submitted by the marketing authorisation holder Janssen-Cilag (local representatives A.M.Mangion) outlining the new recommendations on dosing, duration and precautions for treatment of patients with Nosocomial Pneumonia with Doribax. This letter will be distributed in July to Urologists, Surgeons, the Pharmacy Department and the Medicines Information Unit at Mater-Dei Hospital, private-hospital Doctors, Infectious Disease Specialists and Infectious Disease Prevention and Control Unit in Malta.

Prescribers are also advised that;

- A dose of 500 mg Doribax may not be sufficient for all patients with nosocomial (including ventilator-associated) pneumonia. A dose of 1 g Doribax every eight hours infused over four hours may be considered for patients with augmented renal clearance, and/or infections by non-fermenting gram-negative pathogens such as *Pseudomonas* spp. and *Acinetobacter* spp.
- 10 - 14 days treatment with Doribax is usually needed for patients with nosocomial pneumonia, and is usually in the upper range for patients infected with non-fermenting gram-negative pathogens.
- If non-fermenting gram-negative pathogens are confirmed, doctors should consider concomitant treatment with an aminoglycoside.

Advice for Patients

- Patients are advised that Doribax continues to be a safe and effective antibiotic treatment option for pneumonia caught in hospital (including when the patient is being helped to breathe with a ventilator) and certain other serious bacterial infections.

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- Patients should note that the prescribing information for Doribax has been updated to allow using a higher dose in certain patients with hospital-acquired pneumonia and to clarify certain recommendations for prescribers.
- Patients who have any questions should speak to their doctor or pharmacist.

For more information please see the **press release** and **question-and-answer document** issued by the European Medicines Agency and the current European public assessment report for Doribax which can be found on the Agency's website: **ema.europa.eu/Find medicine/Human medicines/European public assessment reports.**

Reporting adverse drug reactions

Healthcare professionals and patients are encouraged to maintain vigilance on Doribax Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority yellow card scheme or online at **http://www.medicinesauthority.gov.mt/pub/adr.doc** or to the marketing authorisation holder or their local representatives.

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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