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Questions and answers on the review of Doribax (doripenem)

Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004

On 21 June 2012, the European Medicines Agency completed a review of Doribax at the request of the European Commission, after a clinical trial with Doribax in patients with ventilator-associated pneumonia was terminated early due to concerns about the effectiveness of their treatment. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Doribax continue to outweigh its risks, but decided that the prescribing information should be updated to allow using a higher dose in certain patients with hospital-acquired pneumonia and to clarify the recommendations on the use of Doribax in different types of bacterial infection.

What is 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 (indications which are not affected by this review). Doribax is given by infusion (drip into a vein).

Doribax has been authorised in the EU since July 2008 and is marketed in all EU Member States as well as Norway, Iceland and Liechtenstein. The current European public assessment report for Doribax can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

Why was Doribax reviewed?

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 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

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(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.

Which data has the CHMP reviewed?

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.

What are the conclusions of the CHMP?

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 with hospital-acquired pneumonia and to clarify the recommendations and warnings on the use of Doribax in different types of bacterial infection.

The full changes made to the information to doctors and patients are detailed here.

What are the recommendations 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.
- 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.

What are the recommendations for prescribers?

- 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.

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