Bundesamt für Sicherheit
im Gesundheitswesen

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Unser Zeichen: PHV-8546648-A-160316
Ihr Zeichen:

PHV issue Cefepim

Sehr geehrte Damen und Herren,

basierend auf der Evaluierung des PSURs im EU-HBD-worksharing Projekt (Verfahrensnummer: PT/H/PSUR/0008/002) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Cefepim– hältigen Arzneispezialitäten aufzunehmen.

Sollten diese bereits aufgenommen worden sein, betrachten Sie dieses Schreiben als gegenstandslos.

Fachinformation

- Section 4.1

The indication “septicemia” should be reworded to:

“Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above”

...

- Section 4.3

The information should be changed to: “Cefepime is contraindicated in patients who have had previous hypersensitivity reactions to cefepime, to any of the excipients listed in section 6.1., to any other cephalosporin or to any other beta-lactam antibiotics agent (e.g. penicillins, monobactams and carbapenems).”

...

- Section 4.4

Sub-headings (e.g. “Hypersensitivity reactions”, “*Clostridium difficile* associated diarrhea”, “Renal impairment”) should be used where necessary to facilitate readability.

The following warnings should be added in the beginning of this section, as follows:

"*Hypersensitivity reactions*

As with all beta-lactam antibacterial agents, severe and occasionally fatal hypersensitivity reactions have been reported.

Before therapy with cefepime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefepime, beta-lactams or other medicinal products.

Cefepime should be administered with caution to patients with a history of asthma or allergic diathesis. The patient must be carefully monitored during the first administration. If an allergic reaction occurs, treatment must be discontinued immediately.

Serious hypersensitivity reactions may require epinephrine and other supportive therapy.*"*

"Antibacterial activity of cefepime

Due to the relatively limited spectrum of antibacterial activity of cefepime it is not suitable for treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment with cefepime (see section 5.1)."

Consequently, the following text should be added in section 5.1 (if not yet implemented):

"The prevalence of resistance in individualized bacterial strains may vary according to the region and time, so it is recommended to obtain local information about the susceptibility of the strains before initiating the treatment.

Regarding the information related to the use in patients with renal impairment, the text marked as strikethrough should be deleted in order to be more concise:

"*Renal impairment*

In patients with impaired renal function~~, such as reduction of urinary output because of renal insufficiency~~ (creatinine clearance ≤ 50 mL/min) or other conditions that may compromise renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms (see sections 4.2~~ Posology and method of administration~~ and 5.2 ~~Pharmacokinetic properties~~).

During post-marketing surveillance, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including non-convulsive status epilepticus), and/or renal failure (see section 4.8~~ – Undesirable effects~~). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded recommendations.

In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after hemodialysis, however, some cases included a fatal outcome."

According to the SmPC guideline, the information about specific interference with laboratory tests should be included in section 4.4 of the SmPC. Therefore, the following text should be included:

"Interference with serological testing

A positive Coombs test, without evidence of haemolysis, has been described in patients treated with cefepime twice daily.

Cephalosporin antibiotics may produce a false-positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehlings solution or with Clinitest tablets), but not with enzyme-based tests (glucose oxidase) for glycosuria. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used."

Section 4.5

The following possible interaction between bacteriostatic antibiotics and beta-lactam antibiotics should be included:

"Concomitant treatment with bacteriostatic antibiotics may interfere with the action of betalactam antibiotics."

Section 4.6

According to the SmPC guideline, the main information on the possible effects of the medicinal product on male and female fertility should be included under a sub-heading "Fertility" in this section. If there are no fertility data at all, then this should be clearly stated.
The following text is proposed:

"Fertility

No impairment of fertility has been seen in rats. There are no data on the use of cefepime in human fertility."

Section 4.7

The information about the adverse events that could interfere with the ability of driving or operating machines should be included as the text underlined:

"The effects of medicinal product on ability to drive and use machines have not been studied. However, possible adverse reactions like altered state of consciousness, dizziness, confusional state or hallucinations may alter the ability to drive and use machines."

If applicable, cross-references to other sections should be added (e.g. sections 4.4, 4.8).

Section 4.8

The following adverse reaction should be added under the SOC 'Immune system disorders' with a frequency 'rare':

Angioedema

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Package leaflet
The package leaflet should be amended accordingly.

Oben angeführte Textabschnitte stellen eine Mindestanforderung dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.

Die Zulassungsinhaber werden aufgefordert, auch die Gebrauchsinformationen diesbezüglich anzupassen und bis **spätestens 15. Mai 2016** eine Variation gemäß
"Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures."

für die Arzneispezialitäten:

- Bezeichnung der ASPEZ (GZ: xxxxxx; Zul. Nr.: x-xxxxx)

beim Institut Zulassung & Lifecycle Management einzureichen.

In der Begründung ist **„PHV-Issue: Cefepim "** sowie die **Geschäftszahl (PHV-8546648-A-160316)** anzugeben.

Mit freundlichen Grüßen
Für das Bundesamt
Mag. Rudolf Schranz