Bristol-Myers Squibb (Pty) Limited

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IMPORTANT

MEDICINE SAFETY INFORMATION

MAXIPIME® 500 mg; 1 g and 2 g injection (28/20.1.1/0722/3/4)

Risk of serious adverse reactions, including encephalopathy, associated with MAXIPIME (cefepime hydrochloride) particularly in patients with renal impairment who received doses that exceeded the dosage recommendations.

21 May 2018

Dear Healthcare Professional,

Bristol-Myers Squibb (BMS) would like to remind you of the importance of MAXIPIME dosage adjustment in patients with renal impairment, including during treatment, as soon as the creatinine clearance is 50 mL/min or less. Serious neurologic adverse events, particularly encephalopathy, have been reported mostly in patients with renal impairment who received dosages that exceeded the recommendations. The BMS safety database (AWARE) identified 891 cases of non-infectious encephalopathy, 396 (44 %) of which were reported in patients with a medical history of renal impairment. Of these 891 reported cases, 151 (17 %) were fatal. The reports provided also indicated that the encephalopathy occurred sometimes despite dosage adjustments for renal function.

Summary

- MAXIPIME is eliminated almost exclusively by renal mechanisms, primarily through glomerular filtration. Therefore, the dosage for patients with renal impairment (**creatinine clearance ≤50 mL/min**) should be adjusted to compensate for a lower rate of renal elimination.
- Risk of **serious neurological adverse events, particularly encephalopathy** (e.g. disturbance of consciousness, confusion, myoclonus and seizures), in patients with renal impairment (creatinine clearance ≤50 mL/min).
    - Most cases occurred in patients with renal impairment who received doses that exceeded the recommended doses, **especially in elderly patients**.
    - Although the neurotoxicity, including encephalopathy, is generally reversible after discontinuation of MAXIPIME and/or haemodialysis, **some cases had a fatal outcome.**
- **Importance of dose adjustment according to the renal function status.**

Further information

Cefepime (MAXIPIME and generics) is a parenteral cephalosporin antibiotic in the cephalosporin family and is indicated for the treatment of bacterial infections caused by cefepime-susceptible organisms.

Cefepime is eliminated almost exclusively by renal mechanisms, primarily through glomerular filtration. It is important to follow the dose recommendations in the package insert and to adjust the dosages, including during the treatment, according to renal function as soon as the patients' creatinine clearance is ≤50 mL/min in order to compensate for the slower rate of renal elimination. This is even more important for elderly patients with renal impairment.

The recommended dose of MAXIPIME in patients with mild to moderate renal insufficiency should be the same as in patients with normal renal function, but **the dosages should be reduced** when creatinine clearance is ≤50 mL/min. Details of the dose recommendations are provided in Table-1 for adults and pediatric patients with body weights >40 kg who have renal impairment.

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Table-1: Maintenance dosing schedule in adult patients with renal impairment

Creatinine clearance (mL/min):	**Recommended Maintenance Dosage**			
>50	**Usual dose, no adjustment necessary**			
	2 g q8h	2 g q12h	1 g q12h	500 mg q12h
30 - 50	1 g q8h	2 g q24h	1 g q24h	500 mg q24h
11 - 29	1g q12h	1 g q24h	500 mg q24h	500 mg q24h
≤10	1 g q24h	500 mg q24h	250 mg q24h	250 mg q24h
Haemodyalisis*	500 mg q24h	500 mg q24h	500 mg q24h	500 mg q24h

* Pharmacokinetic modelling indicates that reduced dosing for these patients is necessary

Patients receiving cefepime who are undergoing concomitant haemodialysis, should be dosed as follows: 1 gram loading dose on the first day of cefepime therapy, and 500 mg per day thereafter. On dialysis days, cefepime should be administered following dialysis. Whenever possible, cefepime should be administered at the same time each day.

For pediatric patients < 12 years of age with renal impairment, an adjustment of the dosage of MAXIPIME should also be considered.

Renal function should be monitored, especially when cefepime is concomitantly used with potential nephrotoxic antibiotics (e.g. aminoglycosides) or strong diuretics.

For more information, refer to the approved South African package insert dated 06 June 2014.

Call for reporting

Healthcare professionals should report all adverse events associated with the use of MAXIPIME to Bristol-Myers Squibb (Pty) Ltd (South Africa) on 0800 444423 or e-mail, Medinfo.SouthAfrica@bms.com, alternatively to the SAHPRA Pretoria Office at Tel: 012 395 9133, Fax: 086 620 7253, Email: adr@health.gov.za, or the National Adverse Drug Event Monitoring Centre at Tel: (021) 447 1618 or Fax: (021) 448 6181.

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Should you have any questions or require additional information regarding the use of MAXIPIME, please contact 0800 444423 or e-mail Medinfo.SouthAfrica@bms.com.

Yours sincerely

Signature of Pharmacovigilance Officer

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