VIBATIV® ▼ (telavancin)

Healthcare Professional's Guide

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Introduction

As the marketing authorisation holder, Clinigen has to fulfill certain post-approval obligations; this education guide is a mandatory condition of the marketing authorisation. It is to inform you of important safety aspects associated with the use of Vibativ® and how to manage these in order to minimize the risk to the patient.

About Vibativ® / Therapeutic indications

Vibativ® is a semisynthetic lipoglycopeptide antibacterial agent and is indicated for the treatment of adults with nosocomial pneumonia (NP) including ventilator associated pneumonia (VAP), known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Vibativ® should be used only in situations where other alternative treatments are not appropriate or have failed (see Summary of Product Characteristics, sections 4.3, 4.4 and 5.1) [1].

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Antimicrobial spectrum of activity for Vibativ®

Vibativ® is active against

- *Staphylococcus aureus* (including methicillin-resistant strains) with an MIC ≤0,12 mcg/ml

Vibativ® is not active against Gram-negative bacteria.

Important risks of Vibativ®

The following important risks that arise with the use of Vibativ® require special attention and patient monitoring. Further details on these and other risks can be found also in the Summary of Product Characteristics in sections 4.3 – 4.9.

Off label use

The benefit/risk balance of Vibativ® in treatment of complicated skin and soft tissue infections was assessed as negative by the CHMP, the EU committee providing scientific opinions on marketing authorisation applications for medicinal products.

Vibativ® should not be used in this or other non-approved indications.

Nephrotoxicity /Renal insufficiency

In the clinical studies, patients with preexisting acute renal failure receiving Vibativ® had an increased risk of death compared with those receiving vancomycin. All-cause mortality was 32/73 (44%) in the Vibativ® group and 16/64 (25%) in the vancomycin group. In patients without acute renal failure at baseline it was 118/678 (17%) and 124/688 (18%), respectively. Therefore the use of Vibativ® is contraindicated in patients with preexisting acute renal failure and in patients with severe renal impairment (CrCl <30 ml/min, including patients undergoing hemodialysis). Dose adjustment is needed for patients with creatinine clearance of 30 to 50 ml/min. See table below.

In pooled clinical studies (nosocomial pneumonia and complicated skin and soft tissue infection), renal adverse reactions were reported more frequently in patients receiving Vibativ® compared with vancomycin (3.8% vs. 2.2%, respectively).

Patient monitoring in renal function

- Renal function should be monitored in all patients receiving Vibativ®
- Renal function (serum creatinine and urinary output for oliguria/anuria) should be monitored daily for at least the first 3 to 5 days of therapy and every 48 to 72 hours thereafter in all patients receiving Vibativ®.
- Initial dose and dosage adjustments during treatment should be made based on calculated or measured creatinine clearance according to the dosing regimen in section 4.2 of the SmPC and the table below. If renal function markedly decreases during treatment, the benefit of continuing Vibativ® should be assessed.
- Caution should be used when prescribing Vibativ® to patients receiving concomitant nephrotoxic medication, those with preexisting renal disease or with co-morbidity known to predispose to kidney dysfunction (e.g., diabetes mellitus, congestive heart failure, hypertension).

Creatinine clearance* (mL/min)	**Dosage regimen**
>50	10 mg/kg every 24 hours
30–50	7.5 mg/kg every 24 hours
<30, including patients undergoing haemodialysis	Contraindicated
*As calculated using the Cockcroft-Gault formula	

Potential Risk of Teratogenicity / Checklist for pregnancy status

The use of Vibativ® is contraindicated in pregnancy.

The pregnancy status of women of childbearing potential should be established prior to dosing with Vibativ®. Women of childbearing potential should use effective contraception during Vibativ® therapy.

Embryo-fetal development studies in animals indicate that Vibativ® has teratogenic potential which manifests primarily as skeletal findings including limb malformations. The potential risk for humans is unknown. Therefore, the pregnancy status of women of childbearing potential should be established prior to dosing with Vibativ® (serum hCG test). A prescriber checklist is available as a peel-off sticker shipped with the product vial to ensure that Vibativ® is not administered before the patient's negative pregnancy status is confirmed.

The checked sticker should be fixed to the patient chart prior to administration of Vibativ®.

Where clinically appropriate, women of childbearing potential must be advised to use effective contraception during Vibativ® therapy.

Patients should be instructed to notify their prescribing physician/healthcare provider if they become pregnant while taking Vibativ®. There is a pregnancy registry for all women who are exposed to Vibativ® during pregnancy. For further information and enrolment, please call **+44 (0) 1748 828375** or email clinigenEU@professionalinformation.co.uk.

Information can also be found at www.vibativ.eu.

QTc prolongation

Caution is warranted when using Vibativ® to treat patients taking medicinal products known to prolong the QT interval. Subjects with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy were not included in clinical trials of Vibativ®.

Other significant risks

Infusion related reactions

Rapid intravenous infusions with glycopeptide antibiotics class have been associated

with red man syndrome-like reactions. Stopping or slowing the infusion may result in cessation of these reactions. To minimize the likelihood of infusion related reactions, the daily dose should be administered over a one-hour period.

Ototoxicity

Ototoxicity has not been studied in patients treated with Vibativ®. Pharmacological class-related ototoxicity cannot be excluded in these patients.

- Patients who develop signs and symptoms of impaired hearing or disorders of the inner ear during treatment with Vibativ® should be carefully evaluated and monitored.
- Patients receiving Vibativ® in conjunction with or sequentially with other medication with known ototoxic potential should be carefully monitored and the benefit of Vibativ® evaluated if hearing deteriorates.

Interference with Clinical Tests

Coagulation testing

Although Vibativ® does not interfere with coagulation, it can interfere with certain tests used to monitor coagulation (see table below), when tests are conducted using samples drawn between 0 to 18 hours after Vibativ® administration to the patient. The recommendation is that blood samples for coagulation tests should be collected as closely as possible prior to a patient's next dose of Vibativ® or consideration given to using a test unaffected by Vibativ®[2].

Coagulation tests affected by VIBATIV	Coagulation tests unaffected by VIBATIV
International normalised ratio	Whole blood (Lee-White) clotting time
Activated partial thromboplastin time	Ex vivo platelet aggregation
Activated clotting time	Chromogenic factor Xa assay
Coagulation based factor Xa tests	Functional (chromogenic) factor X assay
	Bleeding time
	D-dimer
	Fibrin degradation products

Urinary protein excretion

Vibativ® interferes with urine dipstick and quantitative dye methods of assessing

urinary protein excretion. Microalbumin immunoassays are not affected and can be used instead.

Useful contacts

Further information about Vibativ® can be obtained by visiting www.vibativ.eu or via the approved product information available at www.ema.europa.eu

Information on the pregnancy registry can also be obtained by calling Professional Information on **+44 (0) 1748 828375** or email clinigenEU@professionalinformation.co.uk.

Call for reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Suspected adverse reactions should also be reported to Clinigen by fax on +44 (0) 1283 495304 or email PatientSafety@clinigengroup.com.

Pregnancies occurring after treatment with Vibativ® should be reported by calling **+44 (0) 1748 828375** or email clinigenEU@professionalinformation.co.uk.

Further information can also be found at www.vibativ.eu.

References

1) SmPC Vibativ®. The valid product information for Vibativ can be downloaded from the website of EMA (European Medicines Agency): www.ema.europa.eu

2) Ero, M.P., Harvey, N.R., Harbert, J.L., Janc, J.W., Chin, K.H., Barriere, S.L.; Impact of telavancin on prothrombin time and activated partial thromboplastin time as determined using point-of-care coagulometers. Journal of Thrombosis and Thrombolysis, 2013 Oct