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How bacteraemia is reviewed by medicines licensing authorities in Europe

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Abstract

Bacteraemia has not been recognised as a therapeutic indication in Europe since the publication of the Note for Guidance on Evaluation of Medicinal Products for Treatment of Bacterial Infections in 1997 by the European Medicines Agency (EMEA). This standpoint is in sharp contrast to the labelling decisions taken by the US Food and Drug Administration (FDA). In Europe, a site-specific indication, such as treatment of complicated skin and soft tissue infections is considered to cover cases with bacteraemia, but not vice versa. Only cautionary information is presented in the labelling, e.g. if the number of bacteraemia cases in clinical trials has been low enough to be of concern or if the pharmacokinetic characteristics of the drug may not secure sufficient concentrations in blood. Primary bacteraemia is potentially a situation where the described regulatory paradigm may not apply, but this has yet to be tested. The European approach is likely to be increasingly challenged due to the increasing incidence of bloodstream infections, particularly due to resistant pathogens, and the associated high morbidity and mortality.

Keywords: Bacteraemia; Daptomycin; Linezolid; Quinupristin/dalfopristin; Tigecycline; EMEA

1. Introduction

Bloodstream infections are recognised to be a major cause of morbidity and mortality and are increasing in incidence [1]. Crude mortality rates as high as 50% have been reported in critically ill patients [2]. Increasingly complex medical problems affecting host defence, exogenous immunosuppression, frequent use of invasive procedures and the emergence of pathogens resistant to multiple antimicrobials have contributed to an increase in these infections [3–5]. Especially the proportion of infections arising from Gram-positive pathogens has increased significantly [6] and a majority of *Staphylococcus aureus* isolates in intensive care units have been reported to be resistant to methicillin (MRSA) [7]. In addition to MRSA, MRSA isolates showing reduced susceptibility to vancomycin, vancomycin-resistant enterococci (VRE), multi-resistant or extended-spectrum beta-lactamase-producing (ESBL) Gram-negative bacilli are of particular concern [8]. Further, hospital mortality in patients with bloodstream infections caused by, e.g., such commonly encountered pathogens as methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Pseudomonas aeruginosa* remains high [9].

In addition to host- and specific pathogen-related factors, heterogeneity of the population with bloodstream infections is increased by the fact that bacteraemia may be either primary ('cryptogenic') or associated with an anatomic site. This heterogeneity complicates the review of clinical studies of medicinal products for use in patients with bacteraemia. From the medicinal product regulatory perspective in the EU, the consequence coupled with increased requirements for evidence-based decisions has been that bacteraemia is rarely listed in therapeutic indications (labelling) particularly for drugs that have been licensed since the early 1990s.

2. Current guidance for industry

Both the US FDA and the European Medicines Agency (EMEA) have published guidance for industry on development and labelling of anti-infective medicinal products. In

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the EU, the two most relevant documents are the CPMP Note for Guidance on Evaluation of Medicinal Products for Treatment of Bacterial Infections [10], and CPMP Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products [11]. The European guidance covers only general aspects of clinical development and labelling, not specific therapeutic indications and is not binding. However, any deviations will have to be justified and preferably discussed with medicinal product licensing authorities prior to filing a Marketing Authorisation Application (MAA) for a drug or an extension of therapeutic indications.

It is noteworthy that in the European Union (EU), medicinal products may be licensed through three different routes. The Mutual Recognition Procedure (MRP) is based on initial national Marketing Authorisation (MA) in one Member State (MS) with subsequent MRP whereby MA can be granted by other involved MS. The Decentralised Procedure (DCP) entails simultaneous submission of MAA in some or all MS, with one of them acting as Reference Member State (RMS). In both MRP and DCP, the licensing decisions are national, but result in a harmonised labelling across the involved MS. In the Centralised Procedure (CP), the application is submitted to the EMEA, and its scientific Committee for Human Medicinal Products (CHMP), shall review the dossier and give a scientific opinion which will result in a Community-wide Commission decision on MA or its refusal. The EMEA guidance documents are applicable regardless of the procedure used for obtaining MA.

3. How is bacteraemia viewed by European authorities?

Recognised therapeutic indications fall into two broad categories according to the relevant European guideline [10]. These should either be specific to the site of infection, such as pneumonia, with further description of qualifying conditions, e.g. community-acquired, according to the clinical studies performed, or pathogen-specific. For some indications, qualification by uncomplicated or complicated designations may be appropriate if these are sufficiently well defined and agreed terms in view of the site of infection. A pathogen-specific indication may be appropriate when the antibiotic is expected to be active against rare and/or multi-resistant pathogens and the evidence of activity is based on limited clinical data. This approach will also depend on evidence to support extrapolation of efficacy in one type of infection to infections at other anatomic sites. Finally, a combined site- and pathogen-specific indication, such as *Staphylococcus aureus* endocarditis, may be appropriate depending on clinical evidence.

Bacteraemia or bloodstream infection has not been recognised as a self-standing indication in Europe since the first version of the guideline was adopted and published in 1997. This standpoint has been adopted by EU authorities for both primary and secondary bacteraemia and is in marked contrast to the labelling decisions taken by the US FDA. The FDA has accepted bacteraemia as an additional qualifier in connection with site-specific indications, e.g. complicated skin and soft tissue infection including patients with associated bacteraemia. However, the wording of the indication may or may not include bacteraemia depending on the quality of the data and number of bacteraemic patients treated in clinical trials. The FDA has also approved pathogen-specific bacteraemia as an indication.

In essence, the background to the European standpoint is that site- or exceptionally pathogen-specific indications are preferred. A site-specific indication, such as treatment of complicated skin and soft tissue infections is considered to cover cases with bacteraemia. If the number of bacteraemia cases has been low enough to be of concern, or if the pharmacokinetic characteristics of the drug may not secure sufficient concentrations in blood, this will have to be mentioned in other parts of the labelling, usually in the section ‘Special warnings and precautions for use’.

Another background to this regulatory line of thinking is that if a pathogen-specific bacteraemia indication were approved, this might be interpreted to mean that efficacy has been shown regardless of the site of the infection. A drug that is effective in treating skin and soft tissue infections may not be effective in meningitis or pneumonia. Site-specific indications generally require that sufficient and usually dedicated, randomised and well-controlled clinical trials have been performed. Exceptions to this rule can be initial MA based on limited, sometimes even uncontrolled clinical trials if, e.g., a particular type of resistant pathogen is rarely encountered. The possibility then to extrapolate from one indication to others will be decided on a case-by-case basis depending on the number of patients treated, the number of organisms with a defined resistance pattern isolated from patients and knowledge of the pharmacokinetic–pharmacodynamic relationship of the drug.

Primary bacteraemia is potentially a situation where the described regulatory paradigm may not apply. In primary bacteraemia, by definition, an infection focus cannot be identified. Infection foci might become evident only after treatment initiation, but it may be difficult to assign those as primary or secondary to bacteraemia. There are no regulatory precedents in Europe that could be considered relevant in the current context. However, the European approach is likely to be increasingly challenged due to the increasing incidence of bloodstream infections caused by MRSA and MRSA with decreased susceptibility to vancomycin. Furthermore, *Staphylococcus aureus* bacteraemia is associated with a high risk of morbidity, mortality and recurrence [9,12–16] With regards to *Staphylococcus aureus* bloodstream infections, a primary infection site can be identified in the majority, e.g. pneumonia, skin and soft tissue infection or indwelling vascular catheters, with primary bacteraemia accounting for 11–33% of cases [12,13]. This means that a significant proportion of serious infections are not covered by site-specific indications.