Product information for parenteral colistin varies substantially across Europe

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Objectives: Colistin is the first revived antibiotic to undergo substantial ‘redevelopment’ in academic settings. This study investigated the variation and accuracy of information in the summary of product characteristics (SPC) of intravenous colistin products approved in the European Union.

Methods: The dosing, indication and pharmacokinetic information in the SPCs of approved intravenous colistin products in 21 European countries were compared.

Results: In general, some SPCs have been updated over recent years though vital aspects of dosing recommendations, indications and pharmacokinetic information show a rather broad variation. The importance of a loading dose and of a daily dose ≥6 million international units in critically ill patients with good renal function is not considered in all SPCs. The pharmacokinetic section and dosing recommendations for special patient populations require careful review and updating, in order to take account of newly published data.

Conclusions: This study highlights the challenges of integrating new rapidly evolving scientific knowledge into approved SPCs in Europe.

Keywords: antibacterial drugs, dosing, SPCs, regulatory

Introduction

Worldwide, antibacterial resistance has increased dramatically over the last decade and is currently recognized as a major medical challenge in most healthcare settings. Novel antibiotics with activity against important multidrug- or extensively drug-resistant Gram-negative bacteria are not on the horizon and physicians are resorting to old and ‘forgotten’ antibacterial drugs with retained activity. As these old antibiotics have never been characterized in a structured process for drug assessment and regulatory approval, vital issues such as choosing the appropriate dosage regimen are controversial or unknown. When an antibiotic is administered in a suboptimal dosage regimen, the risk of an unfavourable clinical outcome as well as emergence of resistance may be increased. The summary of product characteristics (SPC) is the information that accompanies a pharmaceutical product in Europe and should promote correct, safe and effective use of the drug. The uncertainty and absence of individual clinical experience with old antibiotics underscores the importance of updated and correct information in the SPC as a source of reliable guidance for clinicians.

Since 1995, applications for antibacterial drugs in Europe are mostly approved by the mutual recognition or decentralized procedure resulting in a product that has been assessed and approved at a European level involving at least two European member states. This procedure leads to identical information in SPCs of a given product in all countries where the marketing authorization has been obtained. Prior to 1995, drug products in Europe were approved by national authorities, leading to divergent information in SPCs across Europe. The parenteral product of colistin, an old polymyxin antibiotic that first entered clinical use in the 1950s, is an excellent example of a pharmaceutical product that was approved before the formation of the European Union (EU). The situation relating to parenteral colistin is further complicated by the relatively recent proliferation of generic products across many countries in Europe and some of these products have been registered by the mutual recognition procedure mentioned above. Thus, for colistin parenteral products many SPCs exist across Europe, of which some originated many decades ago and some were approved at the national level while others have more recently come under the umbrella of the mutual recognition procedure.

Colistin is arguably the first case in the antibacterial field where substantial ‘redevelopment’ activities have been driven by academic and clinical investigators, rather than a sponsoring company. As a result of these activities, there is rapidly evolving new non-clinical and clinical knowledge on colistin and it is essential that clinicians are provided with up-to-date information to
promote safe and effective use of the drug. In the EU, the responsibility for updating SPCs usually lies with the marketing authorization holder, though a referral procedure may be initiated by a member state or the European Commission. In a referral procedure, the issue is referred to the European Medicines Agency so that it can make a recommendation for a harmonized position across the EU. Updating and harmonizing SPCs in regard to optimized dosing regimens is especially important for colistin as this drug has a very low therapeutic index and is used as a last-resort option for the treatment of infections caused by Gram-negative pathogens in severely ill patients. Inappropriate dosing may impact the probability of survival, development of nephrotoxicity and emergence of bacterial resistance.

Thus, in view of the multiplicity of colistin parenteral products registered across Europe and the key role of the respective marketing authorization holders in updating SPCs, the objective of this study was to investigate potential differences in SPCs regarding dosing recommendations and indications of generic colistin products in EU member states.

Methods

Forty current SPCs of approved intravenous colistin products in 20 EU member states and Norway were retrieved from publicly accessible web sites of national regulatory authorities, the Heads of Medicines Agencies as well as professional contacts in the medical field, national drug agencies and distributing companies. The SPCs were translated from 17 languages into English and the information regarding dosing, indications and pharmacokinetic (PK) data compared. In Europe, the vial content of the inactive prodrug colistimethate sodium (CMS) and the dosing information are expressed in international units (IU) and in equivalent mg of the chemical compound CMS. One million IU (MIU) of CMS is approximately equivalent to 80 mg of CMS. In European SPCs, the unit of colistin base activity (CBA) is not used (1 MIU is approximately equivalent to 30 mg of CBA).

Results and discussion

An overview of the various recommendations for intravenous colistin products in European countries for indications and dosage for adults, children and patients with reduced kidney function is presented in Table 1. Fifteen companies distribute intravenous colistin products in one or several European countries, whereas one company produces the active pharmaceutical ingredient but also finished dosage forms as lyophilized and dry-filled vials. Colistin products for injection or infusion are available with a strength of 1 and/or 2 MIU.

Although all but three nationally approved SPCs show a version date of 2009 or later, the date does not imply current updated information and is not meaningful in this context. The published knowledge on how to use colistin more efficiently has increased considerably during the past few years and some SPCs reflect the growing evidence database in regard to dosage regimens for CMS, the inactive prodrug of colistin. A maximum daily dose of 6 MIU, for an adolescent or adult (>60 kg) without renal impairment, has historically been essentially the universal recommendation in European SPCs. However, based upon new population PK studies and preliminary clinical results, this upper limit daily maintenance dose is unlikely to be sufficient in most patients with good renal function and/or where the infection is caused by less susceptible pathogens. Consequently, some SPCs have been updated and now propose an upper limit daily maintenance dose of 9 MIU or even up to 12 MIU of CMS for adult or adolescent patients with good renal function (Table 1). Most SPCs still recommend a standard maximum daily dose of 6 MIU and note that a higher dose may be necessary in special situations or that doses up to 9 MIU have been reported in the literature. Interestingly and unfortunately, the SPCs for the colistin products in Slovakia have not been updated and come with a standard dosage recommendation of 3 MIU daily; this is a very low daily dose and would be expected to result in very low plasma concentrations of formed colistin in patients with good kidney function as well as low clinical response rates. The Sanofi-Aventis products marketed in France and Slovakia have very different dosing recommendations that are facilitated by independent national approval systems and should urgently be harmonized. These important differences observed in the dosing regimens and dosage adjustments between different European countries make it difficult to compare the results obtained in clinical and PK studies from those countries that are based on nationally approved dosage regimens. Ongoing debates about the efficacy of colistin compared with other antibiotics or combination therapy demonstrate the problem of comparing studies with a large variety of dosing regimens including insufficient doses.

Recent population PK studies in critically ill patients have revealed that plasma concentrations of colistin, the active antibacterial formed by the hydrolysis of CMS in the body, will increase slowly (over a day or longer) after the first dose in a maintenance dosing regimen. This highlights the importance of initiating therapy with a loading dose of CMS and this is now implemented in some clinical studies but not universally. The vital issue of a loading dose is not addressed in most SPCs. Colistin parenteral products from Profile Pharma and Xellia, which are registered by the mutual recognition process for clinical use in several European countries (Table 1), mention that a loading dose of up to 9 MIU is suggested in the literature but do not give recommendations regarding the entire dosing schedule, especially maintenance doses and when to start the maintenance schedule. This recent knowledge should be included in future updates. A similar general and vague note of the potential usefulness of a loading dose is included in the Sanofi-Aventis product in France. Only the nationally approved SPC of the product available in Greece provides more detailed information about a loading dose, including mention that the target plasma colistin concentration is dependent upon the MIC for the causative pathogen (Table 1).

If mentioned at all, most SPCs briefly state that the protein binding is low. According to new information, the unbound fraction of colistin A is concentration dependent whereas the unbound fraction of colistin B is constant (average of 43%). Depending on the ratio of colistin A and colistin B, the unbound fraction of both components is 15%–34%. New knowledge is evolving constantly and will need to find its way into the PK section of SPCs.

Similar to the general dosing information in most SPCs, the specific recommendations for patients with impaired renal function do not reflect current knowledge. The criteria for assessing renal function varies among SPCs and may differ from the current regulatory guidance that recommends using glomerular filtration rates to categorize renal function (Table 1). Different classification schemes and absolute or relative cut-off levels impede the
Table 1. Indications and dosage recommendations for adults, children and patients with reduced kidney function in the SPCs of intravenous CMS in selected European countries (August 2013); all doses are expressed in IU of CMS

<table>
<thead>
<tr>
<th>Information in SPC</th>
<th>Supplier (approved in EU member state)</th>
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<tr>
<td><strong>Indication</strong></td>
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<tr>
<td>Nosocomial pneumonia, complicated urinary tract infections</td>
<td>Profile Pharma (AT, DE, DK, ES, IT, NL, SE, UK), Xellia/Novo (AT, DE, DK, ES, IT, NL, NO, RO, SE, UK), Infectopharm (DE), Alfa Wassermann (ES), Alvogen IPCo (BG)</td>
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<td>Serious infections caused by Gram-negative bacteria, including lower respiratory tract and urinary tract infections</td>
<td>Forest (UK, IE, BE, CZ, HU, MT, NL, SK), Beacon Pharmaceuticals (UK), Pharmis Biofarmaceutica (ES), G.E.S. Genéricos Españoles Laboratorio (ES), Generis Farma (PT), Norma (HE), S.C. Antibiotice (RO)</td>
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<tr>
<td>Severe infections such as pneumonia, sepsis, meningitis, urinary tract infections caused by Gram-negative bacteria, especially <em>Pseudomonas aeruginosa</em> and <em>Acinetobacter baumannii</em></td>
<td>Forest (AT)</td>
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<tr>
<td>Microbiologically documented infections in intensive care patients or patients with cystic fibrosis when no other antibiotic is active in vitro</td>
<td>Sanofi-Aventis (FR)</td>
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<td>Acute or chronic infections due to susceptible strains of <em>Enterobacter aerogenes</em>, <em>Escherichia coli</em>, <em>Klebsiella pneumoniae</em> and, in particular, <em>P. aeruginosa</em></td>
<td>UCB Pharma (IT)</td>
</tr>
<tr>
<td>Severe systemic infections caused by susceptible strains of Gram-negative bacteria (e.g. sepsis, urinary tract infections)</td>
<td>Polfa Tarchomin (PL)</td>
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<td>Urogenital infections, ear-nose-throat and respiratory tract infections, intra-abdominal infections, biliary tract infections, sepsicaemia, meningitis, in exceptional cases: ulcers, superinfection of superficial burns and superficial wounds, atitis externa</td>
<td>Sanofi-Aventis (SK)</td>
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<td><strong>Dosage adults</strong></td>
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<td>Up to 60 kg body weight: 50000–75000 IU/kg/day administered in 3 doses &gt;60 kg: 1–2 MIU every 8 h; the standard maximum dose is 6 MIU/day</td>
<td>Profile Pharma (AT, DE, DK, ES, IT, NL, SE, UK), Xellia/Novo (AT, DE, DK, ES, IT, NL, NO, RO, SE, UK), Infectopharm (DE), Forest UK (UK, IE, BE, CZ, HU, MT, NL, SK), Pharmis Biofarmaceutica (ES), G.E.S. Genéricos Españoles Laboratorio (ES), Beacon Pharmaceuticals (UK), Polfa Tarchomin (PL), Generis Farmaceutica (PT), S.C. Antibiotice (RO), Alfa Wassermann (ES), Alvogen IPCo (BG)</td>
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<tr>
<td>6–9 MIU; in severe infections in critically ill patients 9 MIU/day</td>
<td>Norma (HE)</td>
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<tr>
<td>Loading dose (up to 9 MIU) = target concentration of colistin in plasma at steady-state × body weight × 60000 IU; the first dose of the maintenance therapy should be administered 24 h after the loading dose.</td>
<td>Forest (AT)</td>
</tr>
<tr>
<td>Example: in a patient with severe infection, 67 kg body weight, strain with MIC 1 mg/L and target concentration of colistin in plasma at steady-state 2 mg/L, the loading dose is ~8 MIU</td>
<td>UCB Pharma (IT)</td>
</tr>
<tr>
<td>60000–75000 IU/kg/day administered in 2–3 doses (~2 – 5 (~10) MIU/day) Susceptible organisms: 1 MIU daily every 8 h Pathogens with reduced susceptibility: up to 150000 IU/kg body weight (equivalent to 10 MIU for an adult)</td>
<td>Sanofi-Aventis (FR)</td>
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<tr>
<td>50000 IU/kg/day administered in 2–4 doses Elderly (due to decreased renal function): 25000–30000 IU/kg/day, max. daily dosage 100000 IU/kg/day</td>
<td>Sanofi-Aventis (SK)</td>
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<tr>
<td>75000 – 150000 IU/kg/day, administered in 1–3 doses, max. 12 MIU/day</td>
<td>Sanofi-Aventis (SK)</td>
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<tr>
<td>50000 – 100000 IU/kg/day, i.e. usually 3 MIU/day administered in 2–3 doses</td>
<td>Sanofi-Aventis (SK)</td>
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Table 1. Continued

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<th>Information in SPC</th>
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**Dosage in renal dysfunction**

Based on the total daily standard dose of 3–6 MIU/day

- **CLCR (%) of normal value:**
  - 76–100 (normal): 1.3 – 2 MIU every 8 h, total daily dose 4 – 6 MIU
  - 40–75 (mild): 1 – 1.5 MIU every 12 h, total daily dose 2 – 3 MIU
  - 25–40 (moderate): 1 MIU every 12 – 24 h, total daily dose 1 – 2 MIU
  - <25 (severe): 1 – 1.5 MIU every 36 h, total daily dose 0.6 – 1 MIU

- **CLCR:**
  - 20–50 mL/min (mild): 1 – 2 MIU every 8 h
  - 10–20 mL/min (moderate): 1 MIU every 12 – 18 h
  - <10 mL/min (severe): 1 MIU every 18 – 24 h

- **CLCR (%) of normal value:**
  - 40–75: 1–1.5 MIU every 12 h, total daily dose 2–3 MIU
  - 25–40: 0.8–2 MIU every 12–24 h, total daily dose 1.5–2 MIU
  - 25: 1–1.5 MIU every 36 h, total daily dose 0.6–1 MIU

- **CLCR:**
  - 30 mL/min: normal dosing regimen
  - 10–20 mL/min: 30000–50000 IU/kg every 12–18 h
  - <10 mL/min: 30000–50000 IU/kg every 18–24 h

- **Loading dose up to 9 MIU**
  - Maintenance dose: total daily dose = target concentration of colistin in plasma at steady-state × (1.5 × CLCR + 30) × 30000 IU

  Example: MIC 1 mg/L and concentration of colistin at steady-state 2 mg/L:
  - **CLCR:** 40 mL/min/1.73 m²: 5.4 MIU/day
  - **CLCR:** >10 mL/min/1.73 m²: dosing interval 12 or 8 h
  - **CLCR:** <10 mL/min/1.73 m²: dosing interval every 12 h

- **Dosing recommendations for haemodialysis or continuous renal replacement therapy** are detailed in the SPC

  - **SCr:**
    - 1.3 mg/100 mL: 60000–75000 IU/kg/day (daily dose 4.2–5.3 MIU/day)
    - 1.3–5 mg/100 mL: 15000–30000 IU/kg/day (daily dose 1–2 MIU/day)
    - >5 mg/100 mL: 50000–100000 IU/kg/day (daily dose 3–6 MIU/day)

  Anuric patients: single dose (normal dose) with effective concentrations over 5 days

  - **SCr:**
    - 1.5 mg/100 mL, **CLCR:** >80 mL/min: 50000 IU/kg/day, max. 150000 IU/kg/day
    - 1.5–3.5 mg/100 mL, **CLCR:** 30–80 mL/min: 30000 IU/kg/day, max. 60000 IU/kg/day
    - 3.5–10 mg/100 mL, **CLCR:** 20–30 mL/min: 15000 IU/kg/day, max. 30000 IU/kg/day
    - >10 mg/100 mL, **CLCR:** <5 mL/min: 1 MIU every 2–3 days, max. 30000 IU/kg, continuing with up to 1 MIU twice a week

  Anuric patients: 1 MIU after each haemodialysis with max. 30000 IU/kg and continuing with up to 1 MIU after each haemodialysis

  Loading dose of 25000 IU/kg, the maintenance dosage may be adjusted by reducing the dose, while maintaining a fixed interval of 12 h or prolonging the dosage interval and maintaining the fixed dose of 25000 IU/kg

**Paediatric dosage**

Adult dosage or dosage given only for inhalation forms

- **School children (7–12 years):** 1–2 MIU/day
- **Infants (1–6 years):** 0.5–1 MIU/day
- **Infants (up to 12 months):** 0.25–0.5 MIU/day

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Both PK and dosing in special patient populations can be influenced by the presence of renal disease and must be individualized. Evidence-based dosing recommendations in critically ill patients on hemodialysis or on continuous renal replacement therapy are missing or require an update in most SPCs. PK information and recent dosing recommendations in patients receiving different renal replacement therapies are available from recent studies to guide dosage regimens in individual patients. These studies show that both CMS and colistin are cleared by continuous renal replacement therapies and that old dosing recommendations may cause inefficient drug exposure in this patient group.

In general, paediatric dosing recommendations either do not exist for intravenous forms or are not traceable to the source of information. They seem to be arbitrary and may come from the original leaflets. Evidence-based dosing recommendations in children outside the cystic fibrosis area are currently not available and no definite dose of intravenous colistin has been defined for the paediatric age group. Both PK and dosing in special patient populations should be reviewed and updated in all SPCs as soon as high-quality consensus guidelines become available.

PK/pharmacodynamic information on antibiotics is critical for determining their optimal dosage regimens and implementing effective therapeutic drug monitoring (TDM) protocols in critically ill patients with wide PK variability. In general, the main problem in the PK section of most SPCs is the unchanged original information from decades ago derived from microbiological assays. These assays are not capable of differentiating between colistin actually present at the time of collection of a sample from a patient and the colistin formed from ongoing in vitro conversion from CMS also present in the sample at the time of its collection. Colistin concentrations that are measured with methods that cannot differentiate between CMS and formed colistin and are confounded by ex vivo conversion of CMS into colistin in the sample will be artificially higher than the actual concentrations present in the patient. Such data from original studies can still be found in most SPCs (e.g. ‘in patients given 2 MIU every 8 h for 12 days the C_max was 12.9 mg/L (5.7–29.6 mg/L) and the C_min was 2.76 mg/L (1.0–6.2 mg/L)’). Such artificial concentrations are noted in almost all SPCs as the PK sections are based on very old studies. Such outdated information is especially significant as specific chromatographic methods and appropriate handling and processing of samples are available that minimize ex vivo conversion of CMS into colistin and can measure both compounds and their major components separately. TDM protocols based on such appropriate methods are confronted with outdated PK information in the SPCs. Some SPCs even contain the recommendation to determine serum concentrations but give clinically invalid information about the required target concentrations (‘A concentration between 10 and 15 mg/L = about 125–200 IU/mL CMS should be adequate for most infections’). Details regarding the PK information of individual SPCs can be found at http://epasg.escmids.org.

Globally, a major source of confusion and medication error is unclear or wrong labelling and using the inactive prodrug CMS and active colistin interchangeably. In Europe, this potential for errors is limited as all countries label the products as CMS and use IU to describe the amount of drug in the vial and use IU for dosing recommendations. In many regions outside of Europe, the convention to describe the contents of parental vials and corresponding doses for CMS is CBA, which is expressed in mg. If the European convention of describing the amount of CMS as IU is enriched by a further terminology of mg of CMS, the potential for confusion is considered as the units of mg of CMS are not equivalent to mg of CBA (CBA corresponds to ~2.7 x CMS). Many European SPCs and vial labels contain both IU and mg to express the content of CMS. In the age of globalization and worldwide exchange of information, European SPCs and labels may contribute to improved safety by describing the content of vials and posology using only IU of CMS and not mg of CMS.

In European countries, colistin is usually approved for either defined infections (urinary tract infections and pneumonia) or covers a broader field of Gram-negative infections, mostly mentioning that colistin should only be considered if other antibiotics are not indicated or not active (Table 1). Only the recently updated SPC of the nationally approved Sanofi-Aventis product in France does not list any specific indication and reflects the recommended

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**Table 1. Continued**

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<tr>
<th>Information in SPC</th>
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<tr>
<td>Infants: 150 000 – 225 000 IU/kg/day administered in 1 – 3 doses, max. 12 MIU/day</td>
<td>Sanofi-Aventis (FR)</td>
</tr>
<tr>
<td>In children, neonates and premature infants: 50 000 – 100 000 IU/kg/day administered in 2 – 3 doses</td>
<td>Sanofi-Aventis (SK)</td>
</tr>
<tr>
<td>50 000 IU/kg/day administered in 3 doses, max. 75 000 IU/kg/day</td>
<td>Norma (HE)</td>
</tr>
<tr>
<td>Children &lt;2 years: 500 000 – 1 MIU every 12 h</td>
<td>Generis Farmacéutica (PT)</td>
</tr>
<tr>
<td>Children &gt;2 years and adults: 1 – 2 MIU every 12 h</td>
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AT, Austria; BE, Belgium; BG, Bulgaria; CZ, Czech Republic; DE, Germany; DK, Denmark; ES, Spain; FR, France; HE, Greece; HU, Hungary; IE, Ireland; IT, Italy; MT, Malta; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SK, Slovakia; UK, United Kingdom; SCr, serum creatinine.

*a Approved products are not necessarily available in the mentioned country.

*b More than one product with different information may be available in a country. Norway has been included as an associated state.

c The use of a loading dose and/or higher than standard doses (up to 9 MIU) is mentioned in the SPC.
clinical practice to use colistin only in infections due to extensively drug-resistant Gram-negative bacteria where most other antibiotics are not active. The indication section of colistin SPCs would benefit from harmonization across Europe and strengthening the aspect of last-resort therapy.

In conclusion, some SPCs in EU member states have been updated to reflect the growing need for the revived last-resort antibiotic colistin and the accompanying academic ‘redevelopment’ activities. Others still contain confusing or wrong information, especially in the posology and PK section. Colistin is a typical example of the rather new phenomenon of reviving old drugs and the challenge for regulators and generic companies of keeping up with emerging knowledge that is generated outside the pharmaceutical industry. Colistin administered as CMS is a very complex drug with a low therapeutic index and there is great potential for confusion and medication errors. Due to substantial gaps in the knowledge, colistin has been used for several years in an inadequate and suboptimal way, paving the path for clinical failure and the rapid emergence of resistance. As the demand for this drug will continue to increase, a concerted effort to integrate growing knowledge in the SPCs, correct wrong PK data and harmonize information across Europe would benefit the most vulnerable patient group with severe infections caused by extensively drug-resistant Gram-negative bacteria.

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Transparency declarations
None to declare.

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