Daptomycin (Cubicin)
in patients with complicated skin
or soft-tissue infections

INTRODUCTION
Skin and soft-tissue infections (SSTIs) are commonly observed and differ in terms of site and localization, clinical characteristics, and the aetiological agent; these infections are usually caused by *Staphylococcus aureus* or beta-haemolytic streptococci, and are the most frequent forms of methicillin-resistant *S. aureus* (MRSA) infections. SSTIs are considered complicated if they involve deeper skin structures (fascia or muscle layers), require significant surgical intervention or arise in the presence of significant co-morbidity. The progressive increase of bacterial resistance, in particular for Gram-positive bacteria infections, to currently used agents is a serious and growing problem, and in particular MRSA, GISA (glycopeptides-insusceptible *S. aureus*), VRE and GRE (glycopeptides-resistant enterococci) are of concern. There is, therefore, a need for additional agents active against these difficult-to-treat pathogens.

INDICATIONS AND DOSING
Daptomycin (DPT) is a novel macrocyclic lipopeptide antibiotic for the treatment of complicated skin and soft-tissue infections caused by multi-resistant gram-positive bacteria. The drug is derived from a natural product of *Streptomyces roseosporus*, and is active against methicillin-resistant staphylococci and vancomycin-resistant enterococci. Recently, DPT obtained the indication for *Staphylococcus aureus* bacteraemia (SAB) when associated with right-sided infective endocarditis (RIE) or with SSTIs, and for RIE due to *Staphylococcus aureus*. DPT is approved at the recommended dose of 4 mg/kg for SSTIs and at a higher dose for bacteraemia or endocarditis (6 mg/kg), and must be administered as a single daily dose for 7-14 days or until the infection is resolved. The drug is active against Gram-positive bacteria only; if mixed infection (Gram-negative or anaerobic bacteria) is suspected, it should be co-administered with appropriate antibacterial agents. This drug is currently included by AIFA (Agenzia Italiana del Farmaco) in a drug efficacy and safety monitoring program.

PHARMACOKINETICS
DPT is prevalently excreted by the kidneys: therapeutic response and renal function should be closely monitored in patients with renal insufficiency, and dosage adjustment is needed if Ccr is less than 30 ml/min. There is no evidence of hepatic metabolism with involvement of CYP450 enzymes, or of biological activity for metabolites.

PHARMACODYNAMICS
DPT exerts its antibiotic action by inserting into the cytoplasmic membrane of Gram-positive bacterial cells and causing the dissipation of membrane electrical potential, which results in

<table>
<thead>
<tr>
<th>Absorption and distribution</th>
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<tr>
<td>Cmax</td>
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<td>54.6 mg/l (10.0)</td>
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<th>Elimination</th>
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<tr>
<td>Plasma terminal half-life</td>
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<tr>
<td>9.6 (13.5) ml/h/kg</td>
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Table I
Mean (%CV) value for absorption, distribution, metabolism and elimination of DPT after administration of a single dose
bacterial cell death. Bactericidal activity is concentration-dependent against *S. aureus* and vancomycin-resistant enterococci; there is also a concentration-dependent post-antibiotic affect against *E. faecalis* and *S. aureus*.

**EFFICACY AND SAFETY**

Efficacy and safety of DPT in SSTIs were compared with those of conventional antibiotics in two pivotal studies having similar but not identical design, including patients with SSTIs suspected to be due to Gram+ bacteria. One of them was conducted in USA and South Africa, and the other prevalently in European countries.

The appropriate comparator (penicillase-resistant penicillins or vancomycin) was chosen prior to randomization; both protocols provided for a switch to oral medication when certain criteria were met, and the duration of iv therapy was 7 to 14 days, extensible on demand. Population for analysis was distinguished in ITT (Intent-To-Treat, all the treated population with SSTIs), MITT (Modified Intent-To-Treat, patients infected with a Gram+ pathogen), and CE (Clinically Evaluable).

### Table II

**Summary of main studies investigating efficacy and safety of daptomycin in patients with skin or soft-tissues infections**

* naftillin, cloxacillin, flucloxacillin or oxacillin

CE = clinically evaluable population; COMP = comparator; DPT = daptomycin; MITT = Modified Intent-To-Treat population; SSP = penicillase-resistant penicillins; VNC = vancomycin

### Table III

**Daily pharmaceutical costs for different available therapies for SSTIs treatment [Informatore Farmaceutico 2008]**

* only for 1st day of therapy

**price neglects further negotiated discount on supplies for NHS**
CE (Clinically Evaluable, all treated patients for whom the clinical outcome reflected the effect of the study compound): CE patients can be judged as clinical successes if they resulted as cured (return to the pre-infection baseline, with resolution of clinical signs and symptoms) or improved (partial resolution of the infection and no need of further antibacterial therapy) after receiving the study medication for at least 4 days, and having not received other antibiotics. The primary objective was to demonstrate non-inferiority of DPT, reached if the difference in success rates between treatment groups was less than 10%.

Results showed that success rates were numerically similar between the two treatments, and also comparable in sub-groups (severe infection, surgical intervention, bacteraemia), but lower for DPT-treated patients in the subgroup with over 65 years. Duration of therapy resulted lower in DPT-treated patients (63% versus 33% required only 4-7 days of therapy, \( p<0.0001 \)). Safety also appeared comparable between DPT and conventional therapy, whereas a rapid elevation in CPK levels was seen in 2.1% of DPT and only in 1.4% of comparator-treated patients. Skeletal muscle toxicity (seen in early studies), renal risk and the use of this drug in aged population (where an higher incidence of adverse effects has been seen) will be monitored in further studies.

**ECONOMIC EVALUATIONS**

We found only one analysis assessing cost outcomes associated with the use of DPT in SSTIs; this study, performed by Fossaceca and colleagues in 2007, analyzed the first 50 inpatients treated with DPT in USA, and found an average cost of \$ 727 for DPT course, reduced to only \$ 287 in patients who did not respond to prior antibiotic treatment for a Gram-positive bacterial infection. In patients with renal insufficiency the mean cost is \$ 390, and for patient transitioned to outpatient therapy hospital charges were reduced by an estimated \$ 102,340. Infection was resolved with DPT therapy in 96% of patients; cost savings were determined essentially by early identification of antibiotic failure, first-line use of DPT in patients with SSTIs and outpatient therapy.

In Table III we calculated daily pharmaceutical costs of available therapies for SSTIs treatment. For each formulation we valorized minimum and maximum dosing (from the SPCS or from reference trials), using retail price deduced from Informatore Farmaceutico 2008: we considered always an ex-factory price. For packages with identical price, we considered the less costly one. This is not to be intended as a cost-minimization analysis, but as a simple overview of currently available treatments.

<table>
<thead>
<tr>
<th>Name of the Medicinal Product</th>
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<tr>
<td>Marketing Authorisation Holder</td>
<td>Novartis Europharm Ltd</td>
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<tr>
<td>Active Substance</td>
<td>Daptomycin</td>
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<tr>
<td>Pharmaco-therapeutic Group</td>
<td>Antibacterials for systemic use, Other antibacterials</td>
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<tr>
<td>ATC Code</td>
<td>J01XX09</td>
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<tr>
<td>Date of issue of Marketing Authorisation valid throughout the European Union</td>
<td>19 January 2006</td>
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</table>

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