Doripenem

Doripenem is a new carbapenem similar to meropenem and imipenem but different than ertapenem. Doripenem, like other carbapenems, is stable to most beta-lactamases including ampC beta-lactamases and extended-spectrum beta-lactamases (ESBLs). Doripenem, like meropenem and imipenem, possesses broad-spectrum *in vitro* activity which includes activity against many Gram-positive, Gram-negative and anaerobic bacteria; but lacking activity against *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Stenotrophomonas maltophilia*. Doripenem, like imipenem and meropenem, is different than ertapenem in that its spectrum of activity encompasses hospital-associated pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter spp*. and *Enterococcus spp*.. Doripenem is more active than both meropenem and imipenem versus *Pseudomonas aeruginosa* and *Acinetobacter spp*.. due to its strong affinity for penicillin-binding protein (PBP) targets that are species specific, eg. PBP3 in *P. aeruginosa*.

Like imipenem and meropenem, doripenem is administered intravenously achieving similar peak serum concentrations after 500mg dosing. The volume of distribution and protein binding (~8%) are similar to meropenem and imipenem as is the *in vivo* half live of approximately 1 hour. As with meropenem and imipenem, doripenem is primarily excreted unchanged in the kidney and dosing needs to be adjusted in patients with renal dysfunction. Like meropenem and unlike imipenem, doripenem is stable to dehydropeptidase-1 degradation because of its 1-beta methyl constituent on the carbapenem nucleus and thus does require the addition of cilastatin.

Doripenem has been studied in comparative clinical trials establishing its efficacy and safety in the treatment of a variety of infections including complicated urinary tract infections, complicated intra-abdominal infections, nosocomial and ventilatory pneumonia. In a study of complicated intra-abdominal infections (cIAI), doripenem 500mg q8H was administered as a 1 hour intravenous (IV) infusion versus meropenem which was administered as 1 Gram q8H. In this, double-blind, multicenter, prospective, randomized trial, doripenem and meropenem were found to be non-inferior.

Doripenem was studied in a prospective, randomized, open-label, multicenter study versus piperacillin/tazobactam in nosocomial pneumonia. Patients were randomized to either doripenem 500 mg q8H by a 1 hour IV infusion, or piperacillin/tazobactam 4.5 g q6H by 30min IV infusion. Doripenem was shown to be clinically and microbiologically effective in patients with nosocomial pneumonia including those with early-onset ventilator-associated pneumonia and was therapeutically non-inferior to piperacillin/tazobactam.

Doripenem was compared with imipenem for the treatment of ventilator-associated pneumonia (VAP). In a prospective, multicenter, parallel randomized, active-controlled, open-label study, patients received doripenem 500 mg q8H via a 4 hr infusion or imipenem 500 mg q6H or 1000 mg q8H via 30 or 60-min IV infusions, respectively, for 7-14 days. In VAP, a 4 hr IV infusion of doripenem was clinically efficacious and therapeutically non-inferior to imipenem. In all clinical trials, doripenem has shown to as safe as comparators meropenem, imipenem and piperacillin/tazobactam.

Doripenem has been compared to meropenem and imipenem versus *P. aeruginosa* in resistance selection studies. Five separate studies have all shown that doripenem is less likely than other carbapenems such as imipenem

and meropenem to select for resistance. Similar findings have been reported in clinical trials where doripenem demonstrated greater clinical cure rates in patients with *P. aeruginosa* infections (eg. nosocomial and ventilatory pneumonia) compared to imipenem and less resistance developing during therapy.

Doripenem is a promising new carbapenem with similar properties to those of meropenem although it appears to have more potent *in vitro* activity against *P. aeruginosa* and *Acinetobacter spp*. than meropenem.