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Tebipenem Pivoxil/Tebipenem

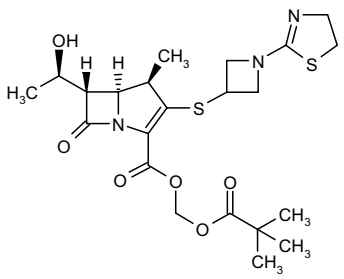
Carbapenem Antibiotic

Tebipenem Pivoxil

Prop INNM; USAN

L-084
ME-1211

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[1-(2-thiazolin-2-yl)azetidin-3-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid pivaloyloxymethyl ester



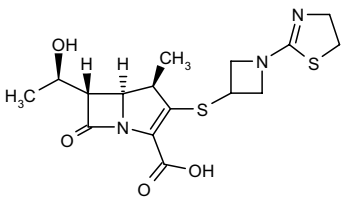
$C_{22}H_{31}N_3O_6S_2$
Mol wt: 497.6302
CAS: 161715-24-8
EN: 268263

Tebipenem

Prop INN; USAN

L-036
LJC-11036

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[1-(2-thiazolin-2-yl)azetidin-3-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid



$C_{16}H_{21}N_3O_4S_2$
Mol wt: 383.4878
CAS: 161715-21-5
EN: 219840

Abstract

Tebipenem pivoxil is a novel oral carbapenem antibiotic candidate, a pivaloyloxymethyl ester prodrug of tebipenem. The potent, broad-spectrum antibacterial activity of tebipenem pivoxil and the active compound has been demonstrated *in vitro* and *in vivo*. Phase II clinical studies of the prodrug are currently ongoing in Japan.

Synthesis

Tebipenem pivoxil can be synthesized by two related methods.

1) Condensation of (phosphoryloxy)carbapenem (I) with 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine (II) affords the thioether adduct (III), from which the *p*-nitrobenzyl ester group is removed by treatment with zinc powder, producing the carbapenem carboxylic acid (IV) (tebipenem). Subsequent condensation of acid (IV) with either iodomethyl (Va) or chloromethyl pivalate (Vb) gives the target compound (1-4). Alternatively, the azetidinoneacetic acid (VI) is condensed with chloromethyl pivalate (Vb) in the presence of NaI and *i*-Pr_2NEt to afford the pivaloyloxymethyl ester (VII), which is then protected as the silyl ether (VIII) by treatment with trimethylsilyl chloride and Et_3N. Dieckmann cyclization of diester (VIII) in the presence of *t*-BuOK and ICH_3, followed by treatment with diphenylphosphoryl chloride, produces the (phosphoryloxy)carbapenem (IX), which is finally coupled with 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine (II) to produce the title compound (5). Scheme 1.

2) The intermediate 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine (II) can be prepared by several different ways. Halogenation of allylamine (X) with either bromine or sulfuryl chloride produces the corresponding (halomethyl)aziridines (XIa,b), which are cyclized to 1-azabicyclobutane (XII) by treatment with butyllithium at –78 °C (1-3). Similarly, conventional bromination of allylamine (X) produces the dibromopropylamine (XIII), which is cyclized to (XII) by distillation in the presence of various bases, including butyllithium (6). Opening of the bicyclic

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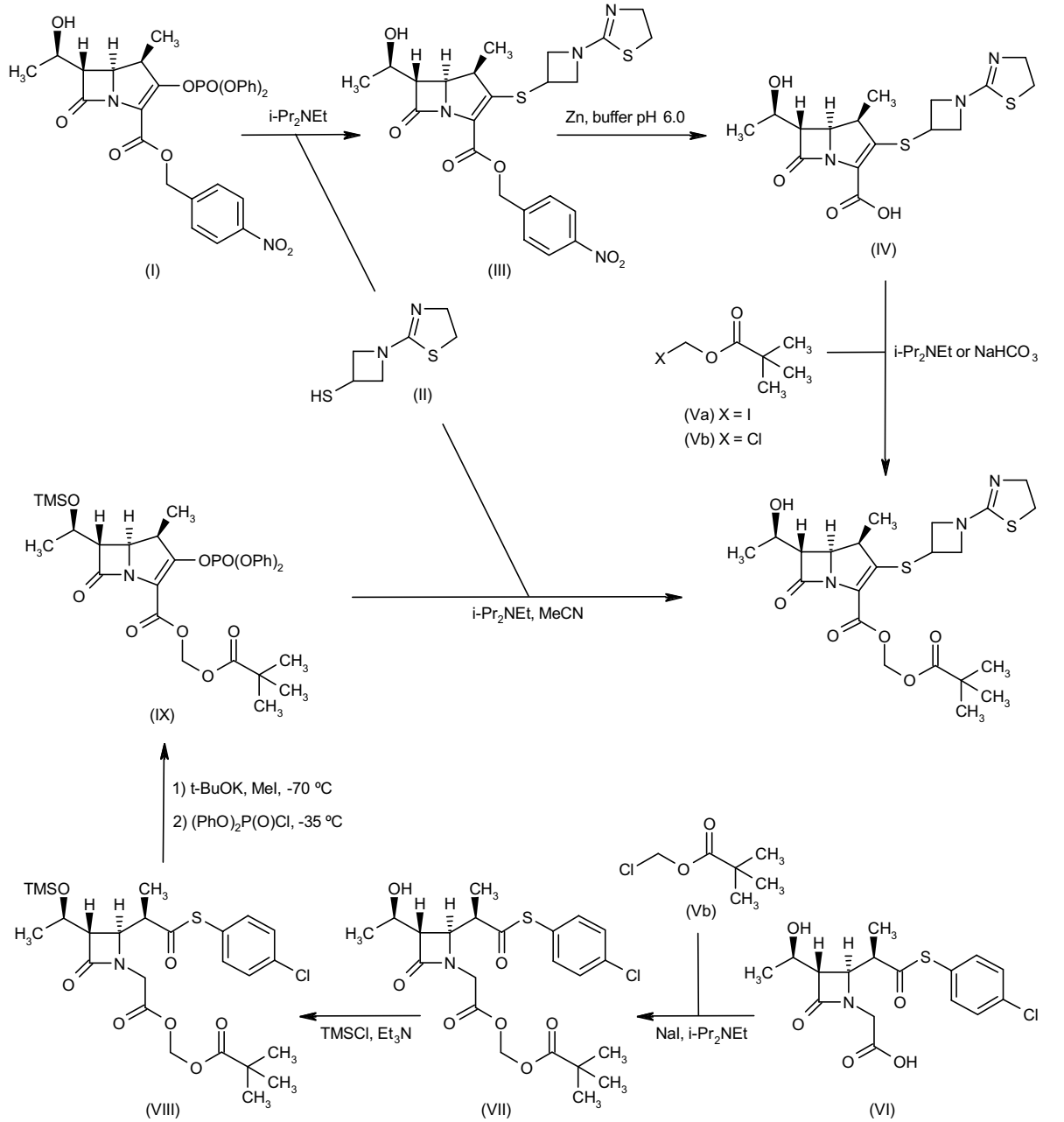
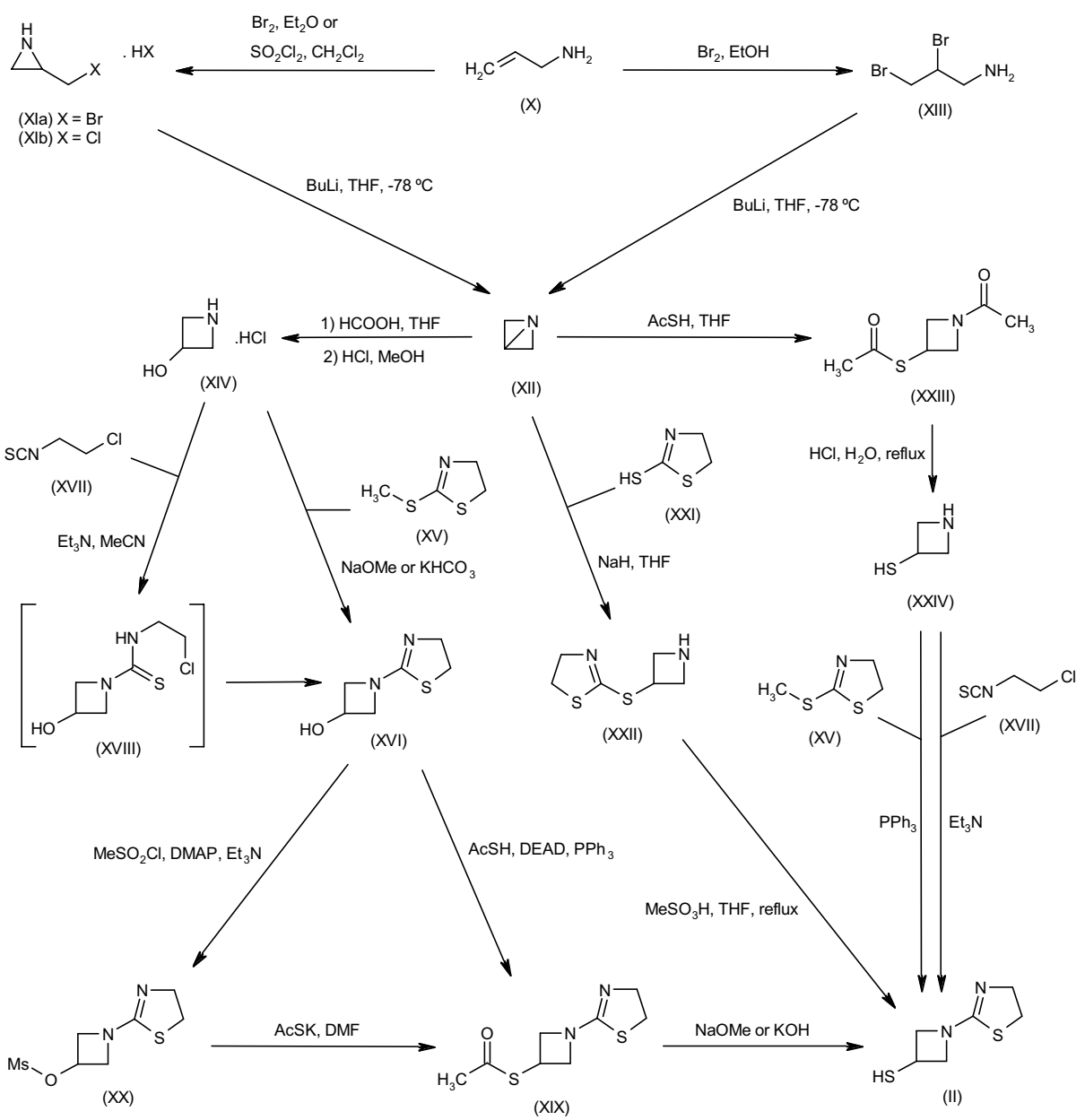
system of (XII) with formic acid, followed by acidic hydrolysis, provides the 3-hydroxyazetidine (XIV), which is condensed with 2-(methylsulfanyl)thiazoline (XV) to give the thiazolinylazetidine (XVI). Alternatively, (XVI) is obtained by condensation of 3-hydroxyazetidine (XIV) with 2-chloroethyl isothiocyanate (XVII) via the intermediate thiourea (XVIII). Conversion of the hydroxyl group of (XVI) to the thioacetate (XIX) is carried out by either coupling with thioacetic acid under Mitsunobu conditions or by conversion to mesylate (XX), followed by displacement with potassium thioacetate. The required thiol (II) is then obtained by basic hydrolysis of the thioacetate ester (XIX) (1-3). An alternative procedure consists of the opening of 1-azabicyclobutane (XII) with 2-mercaptothiazoline (XXI) to give the 3-thiazolinylthioazetidine (XXII), which undergoes rearrangement to the 1-thiazolinylazetidine (II) in the presence of methanesulfonic acid (2). In a further method, 1-azabicyclobutane (XII) is opened with thioacetic acid with concomitant *N*-acetylation, yielding (XXIII). Subsequent acidic hydrolysis of (XXIII) gives

Scheme 1: Synthesis of Tebipenem Pivoxil



Scheme 2: Synthesis of Intermediate (II)



3-mercaptoazetidine (XXIV). Finally, condensation of 3-mercaptoazetidine (XXIV) with either 2-(methylthio)thiazoline (XV) or 2-chloroethyl isothiocyanate (XVII) produces the target thiazolinylazetidine (II) (2, 6). Scheme 2.

Preclinical Pharmacology

Tebipenem pivoxil (L-084, ME-1211) is a novel oral carbapenem antibiotic, the pivaloyloxymethyl ester prodrug of tebipenem (L-036, LJC-11036), which has demonstrated potent and broad-spectrum activity against microorganisms that cause respiratory and urinary tract infections. The prodrug shows high oral bioavailability in rats (38.1% *vs.* 0.8% for tebipenem) and was selected for further development (1, 7, 8).

Tebipenem displayed potent activity against multidrug-resistant *Streptococcus pneumoniae* compared to a panel of other β-lactam antibiotics. Approximately 75% of the clinical isolates tested showed *mefA*- or *ermB*-mediated macrolide resistance, in addition to varying susceptibility to penicillin. For penicillin-susceptible, penicillin-intermediate and penicillin-resistant strains, the

MIC_{90} values for tebipenem were 0.002, 0.004-0.016 and 0.063 μg/ml, respectively. It also exhibited bactericidal activity against resistant strains (8).

The *in vitro* activity of tebipenem against anaerobic bacteria was compared to that of imipenem, cefditoren, amoxicillin/clavulanate and clindamycin. Among all the antimicrobial agents tested, tebipenem showed the best activity, with MIC_{90} values of < 0.03-2 μg/ml against all clinical isolates except *Propionibacterium acnes, Clostridium difficile* and *Bacteroides distasonis*. In particular, tebipenem was 2-16-fold more active than imipenem against clinical isolates of *Peptostreptococcus* spp., *Clostridium* spp., *Fusobacterium* spp. and *Veillonella* spp. Inoculum size had little influence on the antibacterial activity of tebipenem and it was stable to β-lactamases from *Bacteroides fragilis* (9).

In vitro activities of tebipenem against clinical isolates, including vancomycin-resistant *Staphylococcus aureus*, and its binding affinity for penicillin-binding proteins (PBPs) were also compared with those of cefditoren and several other antimicrobial agents. Tebipenem again showed very promising activity against all the organisms tested (MIC_{90} = 0.025-6.25 μg/ml), except vancomycin-resistant *Enterococcus faecium* (MIC_{90} = 100 μg/ml), and a similar pattern of inhibition of PBPs to imipenem, except against PBP2 of methicillin-resistant *S. aureus* (MRSA) and PBP3 of *Escherichia coli*, which was about 10 and 5 times higher than that of imipenem, respectively (10).

The antibacterial activity of tebipenem against clinical isolates from respiratory tract infections, including *S. pneumoniae* (n=52), *Streptococcus pyogenes* (n=19), *Moraxella catarrhalis, Haemophilus influenzae* (n=50) and *Klebsiella pneumoniae* (n=53), was also studied *in vitro*. The antibacterial activity of tebipenem (MIC_{90} < 0.006-0.39 μg/ml) was 2-64 times greater than imipenem, cefdinir and faropenem. Tebipenem also displayed potent activity against various β-lactamase-producing strains, except for carbapenemase producers, and a strong concentration-dependent sub-MIC postantibiotic effect (PAE) against penicillin-resistant *S. pneumoniae* (PRSP) HSC-3 and *H. influenzae* LJ5 (6 h at ¼ the MIC and 9.2 h at ½ the MIC, respectively). The binding affinities of tebipenem for PBP1A, 1B, 2A/2X, 2B and 3 of PRSP HSC-3 were high, with IC_{50} values of 0.12, 0.08, 0.16, 0.05 and 0.01 μg/ml, respectively. The binding affinities of tebipenem for PBP1B, 2, 3A and 3B of *H. influenzae* LJ5 were also very high, with IC_{50} values of 0.09, 0.01, 0.12 and 0.10 μg/ml, respectively. Tebipenem also exhibited excellent activity against urinary tract infection-causing organisms such as *E. coli* (MIC_{90} = 0.05 μg/ml). It was considerably more stable to hydrolysis by renal dehydropeptidases than imipenem. The study indicated that tebipenem has greater activity than imipenem, faropenem and cefdinir against the major organisms causing respiratory and urinary tract infections (11, 12).

A total of 415 clinical isolates of β-lactam-resistant Enterobacteriaceae were tested for their susceptibility to tebipenem, cefpodoxime, ciprofloxacin, tetracycline, fosfomycin and co-trimoxazole. The growth of all isolates was inhibited by tebipenem at 1 μg/ml or less, whereas resistance rates to the comparators ranged from 23% for fosfomycin to 99.5% for cefpodoxime (13).

Tebipenem, imipenem and cefditoren were compared for their activity against clinical isolates of PRSP, methicillin-susceptible and -resistant *S. aureus, E. coli, K. pneumoniae, Citrobacter freundii, Morganella morganii, H. influenzae* and *M. catarrhalis*. Tebipenem was more active than the other antibiotics, with MIC_{90} values of 0.025-6.25 μg/ml, and the compound was bactericidal (14).

The activity of tebipenem, imipenem and oral cephalosporins was compared against *S. pneumoniae, H. influenzae, S. pyogenes, Streptococcus agalactiae* and *M. catarrhalis* isolated from children with respiratory tract infections. Tebipenem was generally the most active agent (MIC_{90} = 0.002-0.25 μg/ml). Bactericidal activity was seen against PRSP (15).

Further *in vitro* studies examined the activity of tebipenem, imipenem, cefdinir, cefditoren and cefpodoxime against clinical isolates of β-lactamase-producing *E. coli* and *K. pneumoniae*. Tebipenem (0.06 μg/ml) was active against all class A and C enzyme-producing isolates except those producing MOX-1, which translated into superior antibacterial activity compared to the other agents, except against class B and MOX-1 producers. No induction of class C enzymes was seen with tebipenem at ¼, 1 and 4 x MIC (16).

Studies using *S. pneumoniae, H. influenzae* and *M. catarrhalis* strains indicated that the activity of tebipenem is greater at lower pH. Most strains were killed by human serum and tebipenem showed synergistic killing with serum (17).

Compared to faropenem, cefdinir, cefditoren and amoxicillin, tebipenem was 4-256-fold more active against penicillin-susceptible or -resistant *S. pneumoniae, M. catarrhalis* and *Legionella pneumophila* (MIC_{90} = 0.032-0.125 μg/ml), and it also displayed activity against *H. influenzae* (MIC_{90} = 0.25 μg/ml). Treatment (10 mg/kg t.i.d. x 3 days) of mice with respiratory tract infections caused by PRSP resulted in a significant decrease in viable counts in lungs, and tebipenem pivoxil was more effective than the other drugs. Although it was substantially less active than cefditoren against *H. influenzae in vitro*, similar efficacy was seen for both agents against murine respiratory tract infections caused by this organism (18).

Tebipenem exerted potent activity against methicillin-susceptible staphylococci, *S. pneumoniae, E. coli, K. pneumoniae, H. influenzae, L. pneumophila* and *M. catarrhalis* (MIC_{90} = 1 μg/ml or less). The prodrug was superior to imipenem, faropenem, cefditoren pivoxil, cefdinir, amoxicillin and levofloxacin against murine respiratory tract infections caused by penicillin-susceptible *S. pneumoniae* TUH39 (ED_{50} = 1.95 mg/kg p.o.), PRSP TUM741 and *H. influenzae* TUM8 (19).

Using a chinchilla model of otitis media caused by PRSP, tebipenem pivoxil proved to be superior to amoxicillin in increasing survival (83% *vs.* 25% and 0% for

amoxicillin and vehicle, respectively), as well as in bacterial eradication and improving otoscopic examination (20).

Pharmacokinetics and Metabolism

Pharmacokinetic analysis of mice with respiratory tract infections demonstrated C_{max}, AUC and $t_{1/2}$ values in lung and serum of 9.03 μg/g and 51.24 μg/ml, 31.0 and 142.2 μg.h/ml and 6.18 and 3.88 h, respectively (19).

In preclinical studies in chinchillas, tebipenem pivoxil showed a C_{max} of 7.2 μg/ml, a t_{max} of 0.67 h and a $t_{1/2}$ of 0.43 h (20).

The pharmacokinetic properties of tebipenem pivoxil were also studied in murine thigh and lung infection models. In the study, pharmacokinetic/pharmacodynamic (PK/PD) parameters that best correlate with the efficacy of tebipenem pivoxil were investigated. In both thigh and lung infection models, AUC/MIC, C_{max}/MIC and the time above MIC all showed a good correlation with efficacy, especially AUC/MIC and C_{max}/MIC (21). These PK/PD findings were confirmed in a phase II study in 112 patients with otolaryngological infections (22).

Pharmacokinetic studies were performed in healthy male volunteers administered single doses of tebipenem pivoxil of 25-200 mg or multiple doses of 100 or 200 mg t.i.d. for 7 days. Following single doses, AUC increased linearly with dose and C_{max} was proportional to dose up to 150 mg; t_{max} and $t_{1/2}$ were both about 30 min. Absorption was not affected by food. Urinary excretion accounted for 54-73% of the dose. Pharmacokinetic parameters were similar after multiple doses, although a metabolite was detected (10% of dose). Good tolerance was seen (23).

Safety

Studies in rats and mice demonstrated that tebipenem pivoxil had little or no effect on cecal flora, in contrast to DU-6859a, which markedly decreased cecal flora in both species, and CS-834, which decreased cecal flora in mice. *In vitro* testing showed that tebipenem pivoxil and CS-834 were stable in cecal contents but their active metabolites were hydrolyzed in rat cecal contents (24, 25).

Clinical Studies

A double-blind phase II clinical study was carried out in 212 patients with otolaryngological infections treated with tebipenem pivoxil at doses of 150 mg t.i.d., 250 mg b.i.d. or 300 mg t.i.d. for 7 days. At the end of treatment, all *S. pneumoniae* and 85.7% of *H. influenzae* were eradicated, irrespective of the dose. Improvement in inflammation was also observed (26). A total of 112 patients were evaluated for efficacy, and analysis revealed efficacy rates of 72.1%, 88.6% and 85.3%, respectively, for doses of 150 mg t.i.d., 250 mg b.i.d. and 300 mg t.i.d. Tebipenem pivoxil showed clinical efficacy in all cases of acute otitis media and in 93.8% of cases of acute sinusitis at the dose of 500 mg. No serious adverse events were recorded, the most frequent being diarrhea and loose stools (13.2% and 14.2%, respectively); adverse events were more common in the group receiving 500 mg/day, the recommended dose (27).

Source

Meiji Seika Kaisha, Ltd. (JP) (licensed from Wyeth Lederle Japan, Ltd.).

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