Linezolid: pharmacokinetic characteristics and clinical studies

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Linezolid is an oxazolidinone indicated in the treatment of nosocomial and community-acquired pneumonia, complicated and uncomplicated skin and skin structure infections and vancomycin-resistant *Enterococcus* infections. The drug is also approved for use in complicated skin infections and nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*, concurrent bacteremia associated with vancomycin-resistant *Enterococcus faecium* and concurrent bacteremia associated with community-acquired pneumonia caused by penicillin-susceptible *Streptococcus pneumoniae*.

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INTRODUCTION

Linezolid is the first member of a new class of synthetic antibacterial agents known as oxazolidinones. This antimicrobial has a potent spectrum of activity against Gram-positive micro-organisms, including multiresistant pathogens. Its mechanism of action is unique (early inhibition of the protein synthesis), so no cross-resistance with other anti-Gram-positive drugs is expected. It can be administered by oral or parenteral route and is well tolerated.

Linezolid was approved by the US Food and Drug Administration (FDA) in April 2000, after which it was approved in Canada and South America. In Europe, linezolid was approved in the UK in February 2001 as well as in Switzerland and in several other non-Union European countries. It is expected to be licensed very soon in the rest of the European Union.

Present indications include nosocomial and community-acquired pneumonia, complicated and uncomplicated skin and soft tissue infections (SSTIs) caused by specified bacteria, and vancomycin-resistant enterococcal infections.

The chemical structure of the drug, its mechanism of action, its spectrum of activity and the data obtained from animal models is discussed in another paper in this issue [1]. We will review herein the pharmacokinetic characteristics of the drug and the available clinical experience, which has been recently summarized in a thorough article published in *Drugs* [2]. Some of the studies we will comment on have already been published, while others are still in abstract form, and some data have been provided by Pharmacia.

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PHARMACOKINETIC PROPERTIES

Administration route and distribution

Linezolid may be administered at the same dose either intravenously (IV) or orally with 100% bioavailability after oral administration. Oral presentations include solution and tablets.

Peak plasma concentrations (C_{max}) are reached 1–2 h after administration (t_{max}). Concomitant administration of food significantly reduces the C_{max} of linezolid (23% reduction) although the area under the plasma concentration–time curve was not affected [2]. The drug has a steady-state volume of distribution of about 40–50 L and is moderately (31%) bound to plasma proteins (Table 1) [3,4].

The studies of intrapulmonary pharmacokinetics of linezolid show that the drug accumulates in epithelial cells (linezolid plasma and lung epithelial lining fluid concentrations were 15.5 and 64.3 mg/L, respectively, 4 h after the dose). Concentrations of linezolid in alveolar cells did not exceed 2.2 mg/L at any measurement point.

Tissue penetration is considered excellent in skin, soft tissue, lung, heart, intestine, liver, urine, kidney and CSF. Penetration is good in synovial fluid, bone, gall bladder and bile. There are no data regarding its presence in breast milk, placental transfer and transfer to fetus.

Dosage and administration

The recommended dosage of linezolid (IV or oral) is 600 mg every 12 h. As mentioned, the drug may be given

Table 1 Pharmacokinetic characteristics of linezolid (modified from [41])

Dose	600 mg per 12 h IV/PO
Serum half life	5 h
Oral absorption	100%
Protein binding	31%
Excretion	Liver 70%/Renal 30%
Active metabolites	50%
Excreted unchanged in urine	30%
Dosing modifications	
Hepatic insufficiency	No
Renal insufficiency	No
Elderly	No
Burns	No
Dialyzability	
Hemodialysis	Yes. 200 mg supplement postdialysis
Peritoneal dialysis	No data

intravenously or orally or switched from the parenteral route to the oral route when the severity of the disease subsides.

In patients with uncomplicated SSTIs the recommended dosage of linezolid is 400 mg/12 h [5].

Patient age or sex did not significantly influence the pharmacokinetic properties of oral linezolid. However, IV linezolid had a shorter half-life in pediatric patients than in adults. Accordingly, the recommended dose of linezolid for infants and children is 10 mg/kg every 8–12 h. However, no clinical studies of linezolid at a dose of 10 mg/kg administered more frequently than every 12 h have been conducted in pediatric patients to date [5]. More data concerning the pharmacokinetics, safety and efficacy of linezolid in children and adolescents (<18 years old) are needed to establish dosage recommendations in this population.

IV linezolid should be infused over a period of 30–120 min. Physical incompatibilities have been demonstrated when linezolid was administered with some drugs, so the recommendation is to administer it separately. Physical incompatibilities resulted when linezolid injection was combined with amphotericin B, chlorpromazine hydrochloride, diazepam, pentamidine, erythromycin, phenytoin sodium or co-trimoxazole. Simultaneous Y-site administration of linezolid injection with one of the five drugs resulting in physical incompatibilities should be avoided [6]. Admixtures of linezolid with ceftriaxone sodium (1 g) exhibited a rapid rate of cephalosporin loss at 23°C, which precludes admixture of the two drugs [7]. Linezolid/ciprofloxacin admixtures should not be stored under refrigeration [8].

Oral linezolid may be taken with small quantities of food or without food, but a high-fat meal decreases the maximum plasma concentration by about 17%. Patients should avoid ingestion of beverages with high tyramine content, mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce.

Metabolism and elimination

Linezolid seems to be primarily metabolized by oxidation of the morpholine ring to form two inactive metabolites. In volunteers, unchanged linezolid accounted for 90% of the circulating dose, with the major metabolite accounting for <6%. Non-renal clearance accounted for 65% of its excretion. At steady state, 30% of linezolid is excreted unchanged in the urine. The elimination half-life was 4.5–5.5 h under single dose and steady state conditions.

Dosage adjustment is not necessary in patients with mild to moderate impaired renal function and liver disease, while patients on hemodyalisis should receive the linezolid dose after the dialysis session or a supplemental 200 mg dose of linezolid at the end of dialysis [9]. The influence of severe hepatic impairment on the pharmacokinetic profile of linezolid has not been established [10].

CLINICAL INDICATIONS

The FDA, however, has not yet approved the use of linezolid in the treatment of infections caused by Gram-positive bacteria (Table 2).

Linezolid is indicated for adults in the treatment of nosocomial and community-acquired pneumonia (CAP), complicated and uncomplicated skin and skin structure infections and vancomycin-resistant *Enterococcus* (VRE) infections. The drug is also approved for use in complicated skin infections and nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*, concurrent bacteremia associated with vancomycin-resistant *Enterococcus faecium* and concurrent bacteremia associated with community-acquired pneumonia caused by penicillin-susceptible *Streptococcus pneumoniae* [11,12]. The FDA, however, has not yet acknowledged the appropriateness of linezolid in the treatment of CAP due to either penicillin-resistant *S. aureus* (PRSA) or MRSA.

CLINICAL EXPERIENCE WITH MULTIRESISTANT GRAM-POSITIVE INFECTIONS

Linezolid is an extremely attractive drug for the treatment of severe infections caused by multiresistant Gram-positive micro-organisms. Its excellent spectrum, its low potential for selecting resistance, the good safety profile and its excellent bioavailability indicate that it should be the drug of choice in this situation. It may be preferred over vancomycin because of the possibility of switching to the oral form and to avoid emergence of vancomycin-resistant enterococci.

Table 2 Clinical efficacy of linezolid vs. comparator drugs in randomized multicenter phase III studies (modified from [2])

Indication	Patients	Clinical cure
MRSA infections [14]	240 LIN 1200 mg	97/103 (94%)
	220 VAN	96/110 (87%)
VRE infections [19]	79 LIN 1200 mg	39/48 (81%)
	66 LIN 400 mg	29/37 (78%)
Pneumonia		
CAP in hospitalized	381 LIN 1200 mg	247/272 (90.8%)
pts [29]	366 CTX/CPD	225/254 (88.6%)
CAP in out-patients [30]	272 LIN 1200 PO	180/201 (89.6%)
Nosocomial [25]	268 CPD PO	187/206 (90.8%)
	203 LIN 1200 + AZN	71/107 (66.4%)
	193 VAN + AZN	62/91 (68%)
Skin and soft-tissue infections		
Uncomplicated [35]	166 LIN 800 mg PO	113/124 (91%)
	166 CLR	114/123 (92.7%)
Complicated [36]	96 LIN or PL	94.4%
	87 FLU + PL	85.3%
Complicated [34]	400 LIN 1200 mg	264/298 (88.6%)
	419 OXA–DIC	259/302 (85.8%)

LIN, Linezolid; VAN, vancomycin; CTX, ceftriaxone; CPD, cefpodoxime; AZN, aztreonam; CLR, clarithromycin; PL, placebo; FLU, flucloxacillin; OXA, oxacillin; DIC, dicloxacillin.

The efficacy of linezolid in the treatment of different infections caused by Gram-positive bacteria has been evaluated in phase II or III clinical trials.

As of January 2000, 671 patients in the USA had received linezolid as part of a noncomparative, nonblind phase II compassionate use program because of intolerance or clinical failure to standard therapy [13]. We will comment on both groups of studies.

Methicillin-resistant *Staphylococcus* species infections

A randomized, multicenter, nonblind phase III clinical trial compared the efficacy of linezolid (240 patients) and vancomycin (220 patients) as treatment for infections caused by methicillin-resistant *Staphylococcus* species (MRSS) [14].

The inclusion criterion was to be a hospitalized patient with bacteremia, SSTIs, urinary tract infections (UTIs), right-sided endocarditis or pneumonia caused by MRSS. Left-sided endocarditis, central nervous system infections and osteomyelitis were exclusion criteria.

Both groups were similar, although the mean age of the linezolid group was greater than that of the vancomycin group (63.9 vs. 58.9 years; $P = 0.02$). Treatment was maintained for 7–28 days.

When analyzed according to the intention-to-treat, overall clinical success rates across all infection types were 56.8% for linezolid (109 of 192 patients) and 55% for vancomycin (93 of 169 patients). However, when patients with missing or indeterminate outcome were excluded, linezolid showed a higher rate of clinical success in patients whom it was possible to evaluate: 94% (97 of 103 patients) vs. 87% (96 of 110 patients) for vancomycin. The high rate of withdrawal seen in this study was attributable to ineligibility (29 linezolid and 34 vancomycin recipients) and death (30 and 22 patients, respectively).

Microbiological success rates were similar (71.9% in the linezolid group and 72.6% in the vancomycin group). Clinical and microbiological success rates analyzed by the different indications were also similar.

The impact on the hospital stay of the switch from IV to oral linezolid was analyzed separately [15]. The objective of the study was to compare length of hospital stay, weekly discharges, and days of antibiotic treatment with linezolid (IV with oral follow-up) and vancomycin (IV only). Four hundred and sixty hospitalized patients with proven or probable infections caused by MRSS were treated with linezolid or vancomycin. The study showed that for linezolid recipients overall hospital stay was slightly, but not significantly, shorter in the overall intent-to-treat group (460 patients) and in the patients that it was possible to evaluate clinically (254 patients). The difference reached statistical significance in the complicated SSTI intent-to-treat (230 patients) and in those patients whom it was possible to evaluate clinically (144 patients) samples (stay 5 and 8 days shorter, respectively). In all samples, linezolid recipients had more discharges in the first week of treatment and fewer days of IV therapy than vancomycin recipients [15].

The efficacy of linezolid in treating MRSA infections has also been assessed in the compassionate use program. One

hundred and sixty patients received the drug because of intolerance to vancomycin (131 patients) or lack of clinical response (29 patients). Syndromes included skin or skin structure infections (28.8%), osteomyelitis (25.0%) and bacteremia (20.6%). Clinical efficacy of linezolid at the end of treatment was 80% for the patients with vancomycin failure and 92% for the group intolerant to vancomycin [16].

Linezolid achieved the sterilization of the respiratory cultures of three lung transplant recipients with MRSA tracheobronchitis after 27–53 days of positive cultures, despite the administration of vancomycin [17]. MRSA respiratory tract colonization recurred, however, in two patients after the withdrawal of linezolid.

Methicillin-resistant *S. aureus* infection in a renal allograft recipient treated successfully with linezolid has also been reported [18].

Vancomycin-resistant *Enterococcus*

The efficacy of linezolid against SSTIs or UTI caused by VRE in hospitalized patients has been investigated in a multicenter, randomized, double-blind study [19]. Exclusion criteria included endocarditis, osteomyelitis or central nervous system infections. Seventy-nine patients received linezolid, 600 mg twice daily, and 66 received linezolid, 200 mg twice daily, for 7–28 consecutive days in this study.

Clinical success rates were 66.7% (42 of 63 patients) in the higher dose group and 53.8% (28 of 52 patients) in the lower dose group. When selecting the patients whom it was possible to evaluate clinically, clinical success reached 81% (39 patients) in the higher dose group and 78% (29 patients) in the lower dose sample. Microbiological eradication was achieved in 37 of 42 (88%) clinically evaluable patients whom it was possible to evaluate clinically treated with linezolid 1200 mg/day vs. 23 of 37 (62.2%) in the lower dose group.

The efficacy of linezolid against VRE has also been studied in compassionate studies, including patients with cancer [20], bone marrow transplantation [21] or intra-abdominal infections [13]. Clinical success rates ranged from 75.6% to 87.6% and microbiological success rates from 72.7% to 90.8%.

Other small series of 15 patients with VRE infections was recently reported. Underlying conditions were renal failure ($n = 6$), recent liver transplantation ($n = 5$), surgery ($n = 6$), cancer ($n = 3$), endocarditis ($n = 2$) or human immunodeficiency virus infection ($n = 1$). Linezolid was administered at a dose of 600 mg every 12 h for 5–42 days (mean 20.5 days). Abscess drainage or prosthetic device removal was undertaken. Microbiological cure was achieved in the 10 patients who completed therapy. Mortality was 53%, but the seven patients alive at follow-up were free of infection and no deaths were attributable to the index infection. Adverse events associated with linezolid use were mild leukopenia in one patient and nausea in another [22].

Successful treatment of vancomycin-resistant *Enterococcus faecium* bacteremia with linezolid after failure of treatment with synercid in a bone marrow transplant recipient has been also recently reported [23].

The combination of linezolid and gentamicin was successful in the treatment of a persistent vancomycin-resistant *Enterococcus faecium* bacteremia [24]. However, although linezolid seems to be useful in the treatment of endocarditis, it must be remembered that its activity against enterococci is mainly bacteriostatic.

CLINICAL EXPERIENCE WITH DIFFERENT CLINICAL ENTITIES

Nosocomial pneumonia

Linezolid was compared with vancomycin for the treatment of nosocomial pneumonia in a multicenter randomized double-blind study. Both groups of patients received aztreonam until the presence of Gram-negatives was excluded [25]. A total of 203 patients received linezolid and 193 patients received vancomycin for 7–21 days.

In patients whom it was possible to evaluate, clinical cure rates (71 of 107 [66.4%] for linezolid vs. 62 of 91 [68.1%] for vancomycin) and micro-biological success rates (36 of 53 [67.9%] vs. 28 of 39 [71.8%], respectively) were equivalent between both treatment groups. The most common reasons for discontinuation of treatment in both groups were the presence of Gram-negative pathogens (37 patients), death (31 patients) and lack of efficacy (10 in the linezolid group and 11 in the vancomycin group).

Eradication rates of methicillin-resistant *S. aureus* and safety evaluations were similar between treatment groups. Resistance to either treatment was not detected [25].

Community-acquired pneumonia

The efficacy of linezolid as treatment for community-acquired pneumonia has been evaluated in three open-label or investigator-blinded trials [26–28]. Patients were organized in two groups depending on the total daily dose received: low dose (750 mg/day) and high dose (1125–1250 mg/day). Fifteen to twenty-eight days after the end of therapy, 91% (32 of 35) and 97% (60 of 62) patients whom it was possible to evaluate in the low- and high-dose groups, respectively, were considered clinically cured or improved. Microbiological success was achieved in 17 of 18 (94.4%) and 37 of 38 (97.4%) patients in the high- and low-dose groups, respectively.

The results of two phase III trials are also available; one in hospitalized patients [29] and the other in out-patients [30].

In hospitalized patients, linezolid was compared with cephalosporin continuation or switch therapy. In out-patients, oral linezolid was compared with oral cefpodoxime proxetil [31].

Overall, 481 patients received linezolid and 470 received cephalosporins in these studies. Clinical and microbiological cure were 90% and 89% in linezolid recipients compared with 89.6% and 88% in cephalosporin recipients.

Linezolid was more effective than cephalosporins in the subgroup of hospitalized patients with community-acquired pneumonia complicated by *S. pneumoniae* bacteremia (93% vs. 69.6%) [32].

An open phase II study performed in infant and children with community-acquired pneumonia (66 clinically evaluable) showed a clinical success rate of 95% [33].

Skin and skin structure infections

A randomized, double-blind, multicenter trial was performed to compare the efficacy and safety of linezolid and oxacillin-dicloxacillin in patients with complicated SSTIs [34]. Aztreonam could be added when necessary. A total of 819 hospitalized adult patients were included. In both groups, patients were switched from the IV form of the drugs to the oral presentations when clinical improvement occurred (after at least 3 days of parenteral therapy). Most common etiologic agents were *S. aureus* and *S. pyogenes*.

The clinical cure rates were similar in both groups when considering intention-to-treat populations (69.8% for linezolid and 64.9% for oxacillin-dicloxacillin, respectively; $P = 0.141$) and also when considering treated patients (88.6% of 298 linezolid-treated patients and 85.8% in 302 patients who received oxacillin-dicloxacillin). Microbiological success was also similar (88% vs. 86%). Both agents were well tolerated [34].

As mentioned before, different dosages of linezolid were evaluated in noncomplicated SSTI phase II studies [27]. Patients received either 750 or 1125–1250 mg/day of linezolid. Clinical cure or improvement was achieved in 82 of 94 (87.2%) patients whom it was possible to evaluate on low dose and in 112 of 125 (89.6%) of the high-dose group. Microbiological success was 90% and 82%, respectively.

In the second phase II study, patients received 200 or 400 mg/day of linezolid. Clinical success was obtained in 62 of 82 (75.6%) patients treated with the low dose and in 59 of 66 (89.4%) who received the higher dose [26].

Other phase III trials compared the efficacy of oral linezolid with oral clarithromycin [35] or oral flucloxacillin in patients with uncomplicated or complicated SSTIs [26,36].

Linezolid and cloxacillin achieved similar clinical (94% and 85%) and microbiological (93% and 89%) efficacy in patients with complicated SSTIs [36]. In the comparison with clarithromycin, 332 patients were divided between the two therapy groups. Efficacy was here again quite similar for both drugs (91% linezolid vs. 92.7% clarithromycin) [35].

Osteomyelitis

Patients with osteomyelitis were included in the previously mentioned studies. Apart from these studies, one report of vertebral osteomyelitis successfully treated with linezolid in a patient receiving hemodialysis has been published. The patient presented with persistent methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus* bacteremias [37].

Linezolid may be an excellent option for the treatment of chronic osteoarticular infections due to its complete oral absorption, the good penetration in bone tissue and the wide antibacterial spectrum against Gram-positive micro-organisms. However, we still need more experience assessing its long-term safety and the efficacy in comparison with other agents such as quinolones or cotrimoxazole combined with rifampin.

Other areas of potential interest

Linezolid has a potent in vitro activity against *Mycobacterium tuberculosis*, and against other species of Mycobacteria [38,39] and *Nocardia* sp. Here again its good bioavailability makes it a very exciting alternative for oral prolonged out-patient therapies.

ADVERSE EFFECTS

Linezolid is generally well tolerated. Adverse effects associated with linezolid include diarrhea, headache, nausea and vomiting. In clinical trials, these were usually mild to moderate in intensity and limited in duration. Certain patients should have periodic monitoring of their blood platelet levels while using linezolid (Table 3).

Among the 517 patients included in two phase II studies (SSTIs and pneumonia), 75.6% experienced adverse events (33% considered drug-related). The most common ones were nausea (5.4%), diarrhea (5.2%), tongue discoloration (2.5%), oral candidosis (2.3%), headache (2.3%) and pain at the injection or catheter site (1.4%). Three percent of the patients were withdrawn from the study because of adverse events considered to be drug-related. Of these, $<1\%$ were considered serious (one case each of elevated liver enzymes, atrial fibrillation, worsening renal failure or pancreatitis) [40].

Regarding phase III trials, 2046 patients received linezolid and 2001 patients received another drug for comparison (vancomycin, cefpodoxime proxetil, ceftriaxone, clarithromycin, dicloxacillin and oxacillin). The most frequently reported

Table 3 Adverse drug reactions occurring at frequencies > 0.1%

General body	
Common:	Headache; candidiasis (particularly oral and vaginal candidiasis) or fungal infection
Uncommon:	Localized or general abdominal pain; chills; fatigue; fever; injection site pain; phlebitis/thrombophlebitis; localized pain
Blood and the lymphatic system disorders	
Uncommon:[a]	Eosinophilia, leucopenia, neutropenia, thrombocytopenia
Metabolism and nutrition disorders	
Common:	Abnormal liver function tests
Nervous system disorders	
Uncommon:	Dizziness, hypoaesthesia, insomnia, paraesthesia
Special senses	
Common:	Taste perversion (metallic taste)
Uncommon:	Blurred vision, tinnitus
Cardiovascular disorders	
Uncommon:	Hypertension
Gastrointestinal disorders	
Common:	Diarrhea, nausea, vomiting
Uncommon:	Constipation; dry mouth; dyspepsia; gastritis; glossitis; increased thirst; loose stools; pancreatitis; stomatitis; tongue discoloration or disorder
Skin disorders	
Uncommon:	Dermatitis, diaphoresis, pruritus, rash, urticaria
Urogenital disorders	
Uncommon:	Vulvovaginal disorder, polyuria, vaginitis
Laboratory abnormalities[b] *occurring at frequencies >0.1%*	
Chemistry	
Common:	Increased AST, ALT, LDH, alkaline phosphatase, BUN, creatine kinase, lipase, amylase or nonfasting glucose Decreased total protein, albumin, sodium or calcium Increased or decreased potassium or bicarbonate
Uncommon:	Increased total bilirubin, creatinine, sodium or calcium Decreased nonfasting glucose Increased or decreased chloride
Hematology	
Common:	Increased neutrophils or eosinophils Decreased hemoglobin, hematocrit or red blood cell count Increased or decreased platelet or white blood cell counts
Uncommon:	Increased reticulocyte count Decreased neutrophils

[a]Frequency as reported by clinician. [b]According to definitions applied during clinical trials. Common: ⩾1/100 and <1/10 or ⩾1% and <10%; uncommon: ⩾1/1000 and <1/100 or ⩾0.1% and <1%.

adverse events reported with linezolid and the comparison drugs were diarrhea (incidence across studies 2.8%–11%), headache (0.5%–11.3%) and nausea (3.4%–9.6%) [5].

Thrombocytopenia, normally reversible, is described in 2.4% of the patients (0.3%–10%). It is more common when the drug is administered for more than 2 weeks [5]. It is thus advisable to monitor platelet counts weekly in patients at risk for bleeding complications, those with previous thrombocytopenia, patients receiving other drugs potentially causing a decreased platelet count or function and patients treated for longer than 2 weeks with linezolid.

Linezolid is classified as a pregnancy category C drug and should be used only if the potential benefit outweighs the risk [41]. It is not known if it is excreted in human milk.

Clostridium difficile associated diarrhea seems to be an uncommon complication of linezolid use (0.2%) [42].

Interactions

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and therefore has the potential to interact with adrenergic drugs, such as dopamine or epinephrine, and serotonergic agents.

According to the manufacturer's prescribing information, some recipients of the drug may experience a reversible increase in the pressor response to dopaminergic or vasopressor drugs, or sympathomimetic agents, which should be administered at a reduced dose [5]. Patients using cold decongestants containing pseudoephedrine HCL or phenylpropamine HCL and patients on serotonin re-uptake inhibitors should be careful when taking linezolid [41].

In addition, the oral suspension form of linezolid contains phenylaline, and should be avoided by patients with phenylketonuria [41].

In summary, the manufacturer recommends that Linezolid should not be used in patients taking any drug that inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxacid, selegiline, moclobemide) or within 2 weeks of taking any such drug. Linezolid should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant medications unless there are facilities available for close observation of the patient and monitoring of blood pressure.

1 Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
2 Patients taking any of the following medications: Serotonin re-uptake inhibitors, tricyclic antidepressants, directly- and indirectly-acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents, dopaminergic agents, pethidine or buspirone.

Antibiotic cost

The total daily cost of linezolid at the usual dose of 600 mg per 12 h is approximately $137 for the IV presentation and of $87 for the oral therapy [41].

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