Safety and tolerability of linezolid

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Clinical trials have shown that linezolid (600 mg twice daily in adults) is safe and generally well tolerated for up to 28 days. Drug-related adverse events, which are typically mild to moderate in intensity and of limited duration, include diarrhea, nausea and headache in adults, and diarrhea, loose stools and vomiting in children. Clostridium difficile-related complications with linezolid are uncommon. Linezolid is a weak, reversible monoamine oxidase inhibitor: foods containing high concentrations of tyramine should be avoided, and linezolid should be used with caution in patients taking adrenergic or serotonergic agents or in those with uncontrolled hypertension. In the majority of patients, linezolid has minimal adverse effects on blood chemistry or haematology. There have been case reports of reversible thrombocytopenia, anaemia and neutropenia associated with linezolid therapy. In Phase III studies, 2.4% of patients treated with linezolid and 1.5% of patients treated with comparator drugs developed reversible thrombocytopenia (P = 0.066), but there was no evidence of an increased risk of agranulocytosis, aplastic anaemia or other irreversible blood dyscrasias. Reduced platelet counts were associated with linezolid treatment for ≥2 weeks; complete blood counts should be monitored weekly in patients receiving linezolid for more than 14 days and treatment should be discontinued if there is evidence of myelosuppression.

Introduction

The oxazolidinones are a class of synthetic compounds initially discovered and investigated by E. I. du Pont de Nemours & Co., Inc. in the late 1980s.1–4 These agents had in vitro activity against Gram-positive bacteria but drug development was discontinued, mainly because of serious toxicity in animal models. Subsequently, Pharmacia & Upjohn, Inc. re-investigated these compounds in the 1990s and discovered a new derivative, linezolid, that retained effective antibacterial activity without significant animal toxicity.5–7

Linezolid (Zyvox, formerly U-100766) was the first oxazolidinone to be developed and approved for clinical use in the USA in April 2000 and in the UK in January 2001. It is active against a range of bacteria, but its primary clinical role is the treatment of infections caused by aerobic Gram-positive organisms, including resistant strains such as vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus and penicillin-resistant pneumococci.5–11 Because the oxazolidinones are an entirely new class of antimicrobial, studies on the safety and tolerability of linezolid are of particular importance.

Pharmacokinetics and metabolism

Availability by oral or parenteral routes

A remarkable feature of linezolid is that it has 100% oral bioavailability: nearly identical peak serum concentrations and elimination profiles are achieved when the drug is administered by either the oral or the parenteral route.12,13 This allows treatment to be initiated orally, or intravenously with the option to switch to the oral formulation. With oral therapy the adverse reactions associated with vascular lines are avoided and hospital discharge may occur sooner,14 reducing the risk of nosocomial infections.

Metabolism

Linezolid is widely distributed and is eliminated by both renal and non-renal mechanisms.15 The metabolic breakdown of linezolid has not been fully elucidated,16 but its two major oxidative metabolites do not appear to have significant antimicrobial activity or toxicity. Under steady-state conditions, plasma concentrations of metabolites account for only 25–35% of the linezolid area under the concentration–time curve. Approximately 30% of a linezolid dose is excreted in the urine

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as the parent drug, 55% in urine as metabolites, and 10% in faeces as metabolites.\textsuperscript{15} In healthy volunteers, renal clearance averages 30–50 mL/min, while non-renal clearance ranges from 70 to 150 mL/min.\textsuperscript{15} Therefore, no dose adjustments are required in patients with renal impairment.\textsuperscript{17} However, linezolid should be administered after a haemodialysis session because ~30–40% of the dose is cleared by haemodialysis.\textsuperscript{12,17} Dosage adjustment is also unnecessary in patients with mild to moderate liver disease.\textsuperscript{18}

Effects of age, gender and race on adult pharmacokinetics

Except for renal clearance, which decreased with decreasing creatinine clearance, there were no significant differences in linezolid pharmacokinetics between older (65–75 years of age) and younger (21–38 years of age) healthy volunteers.\textsuperscript{19} In women, linezolid had an ~20% lower weight-adjusted oral clearance compared with men, with no significant differences in mean half-life or volume of distribution. These minor differences did not warrant any dose adjustment based on age or gender. These findings were supported by Phase II and III trial results in which the incidence of drug-related adverse events was not affected by age, gender or race with the exception of vaginal moniliasis in females.\textsuperscript{20}

Paediatric pharmacokinetics

Following preliminary Phase I studies, the linezolid dose selected for Phase II paediatric studies was 10 mg/kg twice daily, up to a maximum of 600 mg daily.\textsuperscript{21} In children less than 40 months of age, linezolid clearance adjusted by body weight was inversely proportional to age.\textsuperscript{21} However, in older children, linezolid had a similar weight-adjusted clearance, weight-adjusted volume of distribution and half-life to that seen in adults.\textsuperscript{21}

Pregnancy and lactation

Linezolid was not teratogenic in mice at the equivalent of four times the normal human dose.\textsuperscript{12} However, increased embryo death, decreased fetal body weight and skeletal developmental abnormalities were observed at doses causing maternal toxicity.\textsuperscript{12} When female rats were treated with 0.64 times the normal human dose of linezolid during pregnancy and lactation, pup survival decreased. Pups that reached maturity and mated showed an increase in pre-implantation embryo loss, with a corresponding decrease in fertility. Because there are no controlled studies in pregnant women, linezolid should be used only if the potential benefits outweigh the potential risks to the fetus. Linezolid and its metabolites are excreted in the milk of lactating rats at concentrations similar to those in maternal rat plasma. It is not known whether linezolid is excreted in human milk, but caution should be exercised when administering linezolid to lactating women.\textsuperscript{12}

Drug interactions

Monoamine oxidase inhibition

Linezolid is a weak reversible monoamine oxidase (MAO) inhibitor and has the potential to interact with adrenergic and serotonergic agents.\textsuperscript{22,23} In Phase I studies in human volunteers, linezolid alone did not affect blood pressure or heart rate.\textsuperscript{23} When linezolid and tyramine were administered together, tyramine doses of 100 mg or more were required to raise systolic blood pressure by 30 mm Hg. No changes in blood pressure were observed when tyramine was given concomitantly in doses within the range of normal dietary intake (<100 mg per meal). When linezolid was administered with the sympathomimetic agents pseudoephedrine or phenylpropanolamine, transient blood pressure increases were observed.\textsuperscript{22} When administered with the serotonergic agent dextromethorphan, no serotonin syndrome-like effects were seen.\textsuperscript{22}

In Phase III studies, ~30% of linezolid-treated patients and controls received agents that could interact with MAO inhibitors.\textsuperscript{20,24–27} In these patients, adverse events were generally mild to moderate, with a low overall incidence and similar rates in both linezolid and comparator groups. Hypertension was reported in 0.3% of the linezolid group and in 0.2% of the comparator group.\textsuperscript{20,26} Of 879 patients who received linezolid and a potentially interacting medication during Phase II or III studies, only one episode of hypertension was thought to be related to concomitant use of an MAOI-interacting drug.\textsuperscript{20} The patient, who was receiving the selective serotonin reuptake inhibitor fluoxetine, was admitted to hospital with hypoxia and pneumonia and had a transient episode of asymptomatic hypertension. However, other manifestations of the serotonin syndrome were not present, and it was unlikely that the episode was an MAO-related interaction.

In Phase II non-comparative paediatric studies, 39% (56/143) of children treated with linezolid also received medications that could interact with MAO inhibitors. Of these patients, 9% (5/56) experienced adverse events possibly related to MAO inhibition; four of these events were fever and one was mild restlessness.\textsuperscript{20}

When linezolid is administered at a dose of 600 mg twice daily, dietary restrictions are not generally required. However, patients receiving linezolid should avoid consuming large amounts of foods containing high concentrations of tyramine, such as aged cheeses, fermented meats, sauerkraut, soy sauce, draught beers and red wines.\textsuperscript{23} Over-the-counter sympathomimetic agents (such as those containing pseudoephedrine or phenylpropanolamine) can be used; but linezolid should be used with caution in patients with uncontrolled hypertension, pheochromocytoma, carcinoid
Safety and tolerability of linezolid

syndrome or untreated hyperthyroidism, since these patients were excluded in clinical trials. Adrenergic agents such as dopamine or epinephrine can be used with linezolid with careful monitoring.

There have been recent case reports of the serotonin syndrome in four patients who were receiving linezolid and selective serotonin reuptake inhibitors. One woman developed serotonin syndrome within 24 h after starting linezolid having discontinued paroxetine 3 days before. Another patient who was receiving linezolid with sertraline was diagnosed with serotonin syndrome after the abrupt onset of acute confusion, visual hallucinations and delusions. She recovered rapidly after stopping sertraline and starting cyproheptadine, a serotonin antagonist. Two patients were treated with selective serotonin reuptake inhibitors and linezolid after bone marrow transplantation. The first developed symptoms of confusion, fatigue and tachycardia, and the second, increased somnolence, delirium and agitation.

Other potential linezolid drug interactions

When treating mixed infections caused by both Gram-positive and Gram-negative organisms, a second agent such as aztreonam may be needed to provide Gram-negative coverage. A Phase I study found no interactions between these two drugs. In vitro studies found that linezolid was neither a substrate nor an inhibitor of the major human hepatic cytochrome P450 isoforms. Therefore, it is unlikely that linezolid will undergo any cytochrome P450-induced drug interactions.

Effect of linezolid on QTc intervals

In preclinical toxicity studies in dogs, ECG data showed that linezolid had no effect on the QTc interval. In Phase I studies in humans, QTc intervals were measured in 20 volunteers who received linezolid and 16 volunteers who received placebo. No abnormalities or prolongation of QTc intervals were identified, and no differences were observed between the drug and control groups. Thus, linezolid does not appear to affect the QTc interval in animals or humans.

Adverse events in Phase III comparator-controlled trials

Safety and tolerability in adults

Phase III comparator-controlled trials evaluated the use of linezolid in the treatment of community-acquired pneumonia, nosocomial pneumonia, complicated and uncomplicated skin and soft tissue infections and infections caused by methicillin-resistant staphylococci. Among these trials, 2046 patients were treated with linezolid and 2001 patients received comparator drugs, which included oxacillin, dicloxacillin, clarithromycin, vancomycin, ceftriaxone and cefpodoxime. Linezolid was administered intravenously or orally in doses of up to 600 mg twice daily for up to 28 days.

A summary of overall and drug-related adverse events is shown in Table 1. Adverse events, including those that were drug related, occurred slightly more often in the linezolid groups than in the comparator groups, and these differences were significant. However, the incidence of serious adverse events, including those that led to drug discontinuation, was similar in the linezolid and the comparator groups, and there were no significant differences in mortality rate. No deaths were attributed to antibiotic therapy. The only serious adverse event reported in ≥1% of patients was pneumonia (1.3% of linezolid-treated patients and 1.2% of comparator-treated patients).

Table 2 shows adverse events attributed to study drug that occurred in ≥1% of patients. The most common adverse events occurred more frequently in the linezolid groups than in the comparator groups (diarrhoea in 4.3% of the linezolid patients, P = 0.074; nausea, 3.4%, P = 0.036; and headache, 2.2%, P = 0.047). These events were not related to the route of administration. Other treatment-related adverse events that occurred in ≥1% of patients included taste alterations (but the
incidence, 1.2%, was not significantly different from that in the comparator group, \( P = 0.117 \), vomiting (1.1%, \( P = 0.008 \) and abnormal liver function tests (1.0%, \( P = 0.010 \)). Vaginal moniliasis occurred in 1.2% of linezolid-treated patients and 0.6% of comparator-treated patients, but this was not significantly different (\( P = 0.085 \)). None of the adverse events that led to drug discontinuation occurred in \( \geq 1.0\% \) of patients.

Serious treatment-related adverse events occurred in 0.4% of patients. In the linezolid-treated patients, these included thrombocytopenia, hypertension, severe vomiting, transient ischaemic attack, abnormal liver function test, pancreatitis and renal failure; and in the comparator groups allergic reaction, hepatitis, pseudomembranous colitis, thrombocytopenia, kidney failure or nephritis, and Clostridium difficile infection. Haematological events associated with linezolid treatment are discussed in more detail below.

Treatment with linezolid is associated with a low incidence of C. difficile-related complications, similar to that seen with other antibacterials. \(^{33}\) Of 4047 patients treated in Phase III trials, four patients (0.2%) treated with linezolid and eight patients (0.4%) treated with the comparators developed C. difficile-related complications. Pseudomembranous colitis was reported in one linezolid-treated patient and one comparator-treated patient; C. difficile diarrhoea or colitis was identified in six comparator-treated patients, but in none of the linezolid-treated patients; and C. difficile toxin (bacterial infection not otherwise specified) was found in three linezolid-treated patients and one comparator-treated patient. \(^{33}\)

Safety and tolerability in children

Two non-comparator-controlled Phase II trials evaluated the safety of linezolid in 143 children with community-acquired pneumonia \(^{34}\) and acute otitis media. \(^{35}\) Combined data from these studies showed that 55.9% (80/143) of patients treated with linezolid had at least one adverse event, 20.3% (29/143) of which were thought to be drug related. The most common drug-related events included diarrhoea [9.1% (13/143)], loose stools [3.5% (5/143)], vomiting [4.2% (6/143)] and rash [2.8% (4/143)]. Of the four patients with a potential drug-related rash, two had nappy rash, one had a papular rash and one had a non-pruritic rash. In five patients (3.5%), adverse events resulted in discontinuation of treatment; this was thought to be drug related in four cases. \(^{20}\) Overall, linezolid was well tolerated in these children.

A Phase III, randomized, open-label, comparator-controlled, multicentre study recently compared the safety of linezolid with that of vancomycin in children (birth to age 12) with known or suspected resistant Gram-positive infections, including nosocomial pneumonia, complicated skin and skin structure infections and bacteraemia. \(^{36}\) The most frequently reported adverse events among the 215 patients randomized to linezolid therapy were fever (14%), diarrhoea (11%) and vomiting (9%), and the most common among the 101 patients randomized to vancomycin were rash (15%), fever (14%) and diarrhoea (12%). Significantly more drug-related adverse events were reported in the vancomycin group than the linezolid group (34% versus 19%, respectively; \( P = 0.0026 \)). The most common vancomycin-related adverse events included red-man syndrome (vancomycin, 10% versus linezolid, 0%; \( P < 0.0001 \)) and rash (vancomycin, 7% versus linezolid, 1%; \( P = 0.0082 \)). Intravenous/oral linezolid thus appeared to be better tolerated than vancomycin in these patients. \(^{36}\) More paediatric studies will further define the optimal dosing regimen and provide additional safety information. Haematological events in children treated with linezolid are discussed in more detail later.

Long-term safety

Long-term exposure data with linezolid are limited because Phase II and III clinical trials allowed up to only 28 days of
therapy. However, in the pre-licence compassionate-use programme, treatment was much more prolonged. These patients had serious underlying diseases and prolonged treatment courses. Patients in one group of 272 were treated for more than 28 days with a mean of 54 days, and in another group, 556 patients were treated for 28 days or less with a mean of 14 days. Linezolid was generally well tolerated. Thirty-eight per cent of courses were associated with drug-related adverse events, the most common of which were mild, reversible gastrointestinal upset and skin reactions. Eleven per cent of patients discontinued linezolid because of intolerance, most commonly because of thrombocytopenia, gastrointestinal disturbances, decreases in haemoglobin/haematocrit and skin reactions.37

Haematological adverse events reported during linezolid therapy have usually occurred during prolonged treatment courses of more than 14 days. In the compassionate-use programme, 7.5% of the 828 patients developed thrombocytopenia, 4.2% a decrease in haemoglobin or haematocrit, 2.2% leucopenia, 0.24% pancytopenia, 0.24% a decrease in reticulocyte count and 0.12% red blood cell hypoplasia. Of the patients with thrombocytopenia, 12 (1.4%) were treated for <14 days, 26 (3.1%) for 14–28 days and 24 (2.9%) for >28 days. The mean time to a 50% reduction in platelets in these patients was 2–3 weeks. All these adverse events were reversible and none resulted in serious complications or bleeding.37 Other haematological adverse events associated with linezolid therapy are discussed in more detail later.

**Effects on haematology and blood chemistry**

**Preclinical and Phase I studies**

In animal toxicology studies, linezolid caused moderate decreases in white blood cell (WBC), red blood cell (RBC) and platelet counts and increases in alanine transaminase (ALT) concentrations. These changes were dose dependent and reversible when linezolid was discontinued. In Phase I studies in human volunteers, haematological changes were uncommon. None of the volunteers receiving low doses of linezolid (<1 g/day) and 2.4% of those receiving high doses (>1 g/day) developed significant changes in haematocrit, platelet or RBC count. Elevated ALT concentrations were observed in 2.5% of low-dose and 9.8% of high-dose subjects. Both haematological and ALT changes were mild and reversible.

**Haematology and myelosuppression**

In Phase III trials in adults, mean WBC, neutrophil and platelet counts were increased at the start of therapy in both linezolid- and comparator-treated patients. This was consistent with infection and these values returned to the normal range as the infection resolved. Mean values remained within normal ranges, and there were no significant differences in the frequency of outlying values between linezolid and comparator groups. The percentages of linezolid- versus comparator-treated patients who developed outlying haematological values are given in Table 3. There were no significant differences between groups; for platelet counts, 2.4% of linezolid

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**Table 3.** Adult patients in Phase III comparator-controlled trials with chemistry assays more than twice the upper limit of normal or haematology assays < 75% of lower limit of normal (<50% lower limit of normal for neutrophils)20

<table>
<thead>
<tr>
<th>Assay</th>
<th>Linezolid (n = 2046) (%)</th>
<th>Comparators (n = 2001) (%)</th>
<th>χ² P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT,a</td>
<td>7.4</td>
<td>7.2</td>
<td>0.874</td>
</tr>
<tr>
<td>AST,b</td>
<td>4.1</td>
<td>5.3</td>
<td>0.063</td>
</tr>
<tr>
<td>lipase</td>
<td>3.9</td>
<td>3.7</td>
<td>0.858</td>
</tr>
<tr>
<td>amylase</td>
<td>1.8</td>
<td>1.5</td>
<td>0.548</td>
</tr>
<tr>
<td><strong>Haematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>haemoglobin</td>
<td>5.4</td>
<td>4.8</td>
<td>0.450</td>
</tr>
<tr>
<td>WBC count</td>
<td>1.6</td>
<td>1.1</td>
<td>0.115</td>
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<tr>
<td>neutrophils</td>
<td>0.8</td>
<td>0.9</td>
<td>0.540</td>
</tr>
<tr>
<td>platelets</td>
<td>2.4</td>
<td>1.5</td>
<td>0.066</td>
</tr>
</tbody>
</table>

aALT, alanine transaminase.  
bAST, aspartate transaminase.  
cWBC, white blood cell.
identified in any of the Phase III trials.38 Bleeding associated
with thrombocytopenia was most pronounced after ≥2 weeks of therapy.38 The mechanism is not known but linezolid is presumed to have a reversible suppressive effect on the bone marrow.37 The higher rates of thrombocytopenia after 14 days of treatment accords with the 7–10 day platelet life cycle. More than half of the adult linezolid patients who developed thrombocytopenia had low platelet counts at baseline; platelet levels decreased gradually during therapy and recovered after treatment was discontinued.37 Serious bleeding problems were not identified in any of the Phase III trials.38 Bleeding associated with thrombocytopenia was not observed in the uncontrolled compassionate-use programme in patients receiving <14 days of linezolid, but it was not clear what role linezolid had in the platelet suppression of these severely ill patients.37

In the Phase II paediatric community-acquired pneumonia study of children aged 1–12 years, 5/78 (6.4%) patients who received linezolid developed reversible neutropenia [absolute neutrophil count (ANC) < 1500 cells/mm³], either during treatment or at the end-of-therapy visit.34 In four of the five children, a decreasing WBC count was observed by day 3 or by the end of treatment, with ANC nadirs ranging from 1020 to 1470 cells/mm³. In these patients, the neutropenia resolved by the end-of-treatment visit or by 7–15 days after discontinuation or completion of therapy.34 In the fifth child, severe neutropenia developed after five doses of linezolid, and the ANC was 58 cells/mm³ 4 days after linezolid was discontinued. However, 11 days after discontinuation, the ANC for this patient was 2730 cells/mm³.

In the Phase III comparator-controlled study of children (birth to age 12) with known or suspected resistant Gram-positive infections, a sub-analysis was performed on reported haematological adverse effects.39 No significant differences were noted between the linezolid and vancomycin treatment groups in the incidence of anaemia (linezolid, 5.6% versus vancomycin, 7.1%) or thrombocytopenia (linezolid, 4.7% versus vancomycin, 2.0%). Haematological results were comparable between treatment groups when assessed by change from baseline to end of treatment and shifts from baseline to the lowest recorded value. The frequency of substantially abnormal haematological values was similar in the linezolid and vancomycin treatment groups: haemoglobin (15.7% versus 12.4%, respectively), platelet count (12.9% versus 13.4%) and ANC (5.9% versus 4.3%). In addition, there were no significant differences in reticulocyte indices, serum iron concentration or transferrin saturation. Overall, the sub-analysis demonstrated no significant differences in haematological effects between linezolid and vancomycin treatment.

Outside the clinical trial data, there have been several case reports in adults of reversible myelosuppression associated with linezolid therapy, including thrombocytopenia, anaemia, red cell aplasia and pancytopenia.40–47 Most of these cases were in patients on prolonged treatment courses and with underlying diseases that predisposed to haematological abnormalities. Despite these case reports, the clinical trial data referred to above show that, in comparison with comparator drugs, linezolid is associated with only a slightly increased (1%) cumulative incidence of thrombocytopenia after 2 weeks of therapy and has no significant association with anaemia or neutropenia.38,48 Nevertheless, Pfizer issued a warning letter about linezolid and myelosuppression in March 200149 and added the following to the warning section of the linezolid labelling:

‘Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression’.12

Patients on prolonged linezolid therapy often have multiple underlying illnesses and other medications that may predispose to myelosuppression. Due to the inherent difficulty in determining the true relationship between linezolid therapy and myelosuppression, longer-term, prospective, randomized trials or retrospective case-controlled studies of linezolid versus other antibiotics are required.

**Blood chemistry**

Changes in blood chemistry were similar in linezolid and comparator groups. Mean values for liver function tests and other blood chemistry were within the normal range through-

**Figure 1.** Phase III comparator-controlled trials: cumulative percentage of patients with at least one substantially low platelet count (<75% of lower limit of normal and/or baseline).38 Adapted with permission from the American Society for Microbiology.
out the course of the Phase III studies, and the proportion of patients with outlying values (i.e. more than twice the upper limit of normal) was similar in the linezolid and comparator groups (Table 3). Changes were reversible after completion of therapy, and few patients discontinued therapy because of laboratory abnormalities.

Overdosage

Linezolid overdoses have not been observed in humans. In rats, a linezolid dosage of 3 g/kg/day was associated with decreased activity and ataxia, and in dogs a dosage of 2 g/kg/day was associated with vomiting and tremors. If human overdose occurs, supportive care with maintenance of glomerular filtration is recommended. Haemodialysis may be helpful because ~30% of a linezolid dose is removed during a 3 h haemodialysis session.12

Conclusions

Linezolid is safe and generally well tolerated in dosages of 600 mg twice daily for up to 28 days. Drug-related adverse events are usually transient and mild to moderate in severity. The most common adverse events in adults are diarrhoea, nausea and headache, and in children, diarrhoea, loose stools and vomiting. Although linezolid is a weak and reversible MAO inhibitor, the clinical effect is minimal, and only moderate dietary restrictions are required. In the majority of patients, linezolid has no adverse effects on haematology or blood chemistry. However, there is evidence of rare, reversible myelosuppression associated with prolonged linezolid therapy, and further studies are needed to clarify the significance of this phenomenon. Complete blood counts should be monitored weekly in patients receiving 14 days or more treatment with linezolid, and therapy should be discontinued if worsening myelosuppression is found. Overall, the drug is well tolerated and has a potentially important role in the treatment of serious Gram-positive infections.

References


Safety and tolerability of linezolid


