LINEZOLID (Systemic)

Indications

Accepted

Pneumonia, community-acquired (treatment)¾Intravenous and oral linezolid is indicated in the treatment of community acquired pneumonia caused by penicillin-susceptible strains of Streptococcus pneumoniaeor methicillin-susceptible strains of Staphylococcus aureus. 1

Pneumonia, nosocomial (treatment)¾Intravenous and oral linezolid is indicated in the treatment of nosocomial pneumonia caused by methicillin-susceptible and methicillin-resistant Staphylococcus aureus or penicillin-susceptible strains of Streptococcus pneumoniae. 1

Skin and soft tissue infections, complicated (treatment)¾Intravenous and oral linezolid is indicated in the treatment of complicated skin and soft tissue infections caused by Staphylococcus aureus (methicillin-susceptible and methicillin-resistant), Streptococcus pyogenes, or Streptococcus agalactiae . 1 Patients with diabetic foot ulcers and decubitus ulcers were not included in the clinical trials. 1

Skin and soft tissue infections, uncomplicated (treatment)¾Oral linezolid is indicated in the treatment of uncomplicated skin and soft tissue infections caused by methicillin-susceptible strains of Staphylococcus aureus or Streptococcus pyogenes. 1

Vancomycin-resistant Enterococcus faecium infections¾Intravenous and oral linezolid is indicated in the treatment of vancomycin-resistant Enterococcus faecium infections. 1

Mechanism of action/Effect:

The mechanism of action for linezolid is different than that of other antibacterial agents; therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely. 1 Linezolid acts via inhibition of protein synthesis. 1 It binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex. 1 This step is essential for the bacterial translation process. 1

Precautions to Consider

Carcinogenicity/Tumorigenicity/Mutagenicity

Although lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of linezolid, no mutagenic or clastogenic potential was found in a battery of tests, including the Ames and AS52 assays, an in vitrounscheduled DNA synthesis (UDS) assay, an in vitro chromosome aberration assay in human lymphocytes, and anin vivo mouse micronucleus assay. 1

Pregnancy/Reproduction

Fertility¾Linezolid did not affect the fertility or reproductive performance of adult female rats. 1 It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ³ 50

mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). 1 Epithelial cell hypertrophy in the epididymis may have contributed to the decreased fertility by affecting sperm maturation. 1 Similar epididymal changes were not seen in dogs. 1 Although the concentrations of sperm in the testes were in the normal range, the concentrations in the cauda epididymis were decreased, and sperm from the vas deferens had decreased motility. 1

Mildly decreased fertility occurred in juvenile male rats treated with linezolid through most of their period of sexual development (50 mg/kg/day from days 7 to 36 of age, and 100 mg/kg/day from days 37 to 55 of age, with exposures ranging from 0.4-fold to 1.2-fold that expected in humans based on AUCs). 1 No histopathological evidence of adverse effects was observed in the male reproductive tract. 1

Pregnancy¾Adequate and well-controlled studies in humans have not been done. 1

Linezolid was not teratogenic in mice or rats at exposure levels 4-fold (in mice) or equivalent to (in rats) the expected human exposure level, based on AUCs. 1

In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). 1 A dose of 450 mg/kg/day (4-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. 1

In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.13- to 0.64-fold the estimated human exposure, respectively, based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. 1

When female rats were treated with 50 mg/kg/day (.64-fold the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss, with a corresponding decrease in fertility. 1

FDA Pregnancy Category C. 1

Breast-feeding

It is not known whether linezolid is distributed into human breast milk. 1

Linezolid and its metabolites are excreted in the milk of lactating rats. 1 Concentrations of linezolid were similar in milk and maternal plasma of rats. 1

Pediatrics

Appropriate efficacy studies on the relationship of age to the effects of linezolid have not been performed in the pediatric population. 1 In this population, linezolid clearance is increased resulting in a shorter half-life. 1 A pediatric dosing regimen that provides comparable pharmacokinetic parameters to the adult regimen has not been determined. 1

Geriatrics

Appropriate studies performed to date have not demonstrated geriatrics-specific problems that would limit the usefulness of linezolid in the elderly. 1

Pharmacogenetics

The volume of distribution and mean oral clearance are lower in females than males; however, the mean apparent elimination-rate constant and half-life are not significantly different between genders. 1 Drug exposure in females is not expected to increase beyond levels known to be well tolerated. 1

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Aztreonam or

Gentamicin

(the pharmacokinetics of linezolid and these antibiotics were not altered 1 )

Dextromethorphan or

(serotonin syndrome did not occur with concurrent administration; other serotonin re-uptake inhibitors were not studied 1 )

Dopamine or

Epinephrine

(initial dose should be reduced and titrated to achieve the desired response 1 )

>> Phenylpropanolamine or

>> Pseudoephedrine

(systolic blood pressure increased by 32 mm Hg and 38 mm Hg after administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively 1 )