Clean Proposed Professional Information for Medicines for Human Use:

AKLID

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

AKLID (film coated tablets)

COMPOSITION

Active ingredient

Each film coated tablet contains 600 mg linezolid.

Inactive ingredients

Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Opadry White (containing hypromellose, macrogol and titanium dioxide), poloxamer, povidone, sodium starch glycolate and talc.

Contains sugar: lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION

A 20.1 .1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Linezolid is a synthetic antimicrobial agent of the oxazolidinone class of antibiotics. It is active against aerobic Gram-positive organisms and has limited activity against most aerobic or anaerobic Gram-negative organisms. Linezolid has bacteriostatic activity against staphylococci and enterococci and has bactericidal activity against streptococci. It

selectively inhibits bacterial protein synthesis by binding to the P site of the ribosomal subunit and in turn preventing the formation of the larger ribosomal complex that initiates the protein synthesis. As a result of its action linezolid is active against resistant strains of organisms. *In vitro* studies have shown that resistance of organisms to linezolid occurs as a result of slow point mutations of the 23S ribosomal RNA of the organisms. Because of the presence of multiple copies of 23S ribosomal RNA, mutations need to occur in two or more copies for an organism to become resistant.

Resistant organisms

Inherently resistant organisms

- *Haemophilus influenzae, Enterobacteriaceae, Neisseria* species and Pseudomonas species.

Intermediately susceptible organisms

- *Legionella* species, *Mycoplasma* species and *Moraxella catarrhalis*.

The mechanism of action of linezolid differs from that of other antibiotics. There is no cross-resistance between linezolid and other classes of medicines, such as aminoglycosides, beta-lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifamycins, streptogramins, tetracyclines and chloramphenicol.

Pharmacokinetic properties

The aqueous solubility of linezolid is approximately 3 mg/ml and is independent of pH between pH 3 and 9.

Absorption

Linezolid is well absorbed after oral administration. It is not affected by food. Peak serum concentrations are reached within 2 hours after a single dose of 600 mg. Absolute bioavailability is 100 %.

Distribution

Linezolid distributes widely to well perfused tissues and is 31 % protein bound.

Metabolism

Linezolid is broken down by non-enzymatic oxidation to hydroxyethyl glycine derivatives and aminoethoxy acetic acid.

Elimination

Under steady state conditions 80 % of linezolid is excreted in the urine and 10 % of the administered dose appears as oxidation products in the faeces. The elimination half-life of the parent drug is averaged between 5 – 7 hours.

The serum concentrations and half-life of the linezolid parent compound are not altered by renal insufficiency. The clinical significance of this is unknown. No dose adjustments for such patients are currently required. Dialysis eliminates linezolid and its breakdown products, therefore the dose should be administered after dialysis treatment.

Due to the metabolism of linezolid by a non-enzymatic process, hepatic impairment is not expected to alter the metabolism and dose adjustments in such patients are not required.

There is wider inter-subject variability in the clearance of linezolid and the systemic drug exposure across all paediatric patients when compared to adults.

INDICATIONS

AKLID is indicated for the treatment of patients with the following infections caused by susceptible strains of the designated microorganisms:

- **Vancomycin-resistant *Enterococcus faecium* infections:** including cases with concurrent bacteraemia.
- **Nosocomial pneumonia:** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant *S. pneumoniae* (MDRSP) strains). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

- **Complicated skin and skin structure infections:** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes* or *Streptococcus agalactiae*. AKLID has not been studied in the treatment of decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.
- **Uncomplicated skin and skin structure infections:** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pyogenes*.
- **Community-acquired pneumonia:** caused by *Streptococcus pneumoniae* (including multi-drug resistant *S. pneumoniae* (MDRSP) strains), including cases with concurrent bacteraemia, or *Staphylococcus aureus* methicillin-susceptible and -resistant strains).

CONTRAINDICATIONS

- Hypersensitivity to linezolid or any of the other ingredients of AKLID (see COMPOSITION).
- AKLID should not be used in patients treated with monoamine inhibitor oxidases A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks after discontinuation of taking such medicines.
- AKLID should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant medications:
  - Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
  - Patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), serotonin-norepinephrine reuptake inhibitors (SNRis), direct and indirect acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressor agents (e.g. epinephrine

(adrenaline), norepinephrine (noradrenaline)), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

- Pregnancy and lactation (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS

Due to concern about inappropriate use of antibiotics leading to an increase in resistant organisms, healthcare practitioners should carefully consider alternatives before starting treatment with AKLID in the outpatient setting.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to AKLID. Therapy may be instituted empirically while awaiting results of these tests. Antimicrobial therapy should be adjusted accordingly once these results become available.

• ***Antibiotic-associated diarrhoea and colitis***

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of AKLID and may range in severity from mild diarrhoea to fatal colitis. In antibiotic-associated colitis, treatment with AKLID should be discontinued. Appropriate therapy should be instituted. Therefore, it is important to consider this diagnosis in patients who develop severe diarrhoea during or after the use of linezolid.

Suspicion of antibiotic-associated diarrhoea and colitis requires immediate cessation of treatment, with appropriate specific antibiotic therapy effective against *Clostridium difficile*. Medicines inhibiting gut motility/peristalsis are contraindicated in this situation.

Superinfections

Patients with mixed Gram-negative and Gram-positive infections are at a higher risk of mortality when linezolid, as contained in AKLID, is given as monotherapy. The use of antibiotics may promote the overgrowth of non-susceptible organisms. Appropriate

measures should be taken if a superinfection occurs during AKLID treatment. AKLID should be given along with appropriate antibacterial cover for Gram-negative organisms in patients with mixed Gram-positive and Gram-negative infections.

Myelosuppression

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid, as in AKLID. Cases of sideroblastic anaemia have been reported post-marketing. Where time of onset was known, most patients had received linezolid therapy for more than 28 days. Most patients fully or partially recovered following discontinuation of linezolid with or without treatment for their anaemia. Full blood counts should be monitored in patients presenting with myelosuppression, including anaemia, leucopenia, pancytopenia and thrombocytopenia, patients who receive other medication causing bone marrow depression, patients with chronic infections and patients who are receiving concurrent antibiotic treatment. Discontinuation of treatment with AKLID should be considered in patients with worsening myelosuppression.

Peripheral and optic neuropathy

Peripheral neuropathy, optic neuropathy and optic neuritis, sometimes progressing to loss of vision, can occur in patients receiving long-term (e.g. 28 days) treatment with AKLID. This may be as a result of the effect of AKLID on mitochondria. AKLID is not recommended for long-term use, as effects have not always been reversible. If symptoms of visual impairment occur while taking AKLID, evaluation is required. Patients should be advised to report symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect. Prompt evaluation is recommended with referral to an ophthalmologist. There may be an increased risk of neuropathies when AKLID is used in patients currently taking or who have recently taken antimycobacterial medications for the treatment of tuberculosis (see INTERACTIONS).

Serotonin syndrome

Spontaneous cases of serotonin syndrome associated with the co-administration of AKLID and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRis)

have been reported. Co-administration of linezolid and serotonergic agents is therefore contraindicated (see CONTRAINDICATIONS).

Lactic acidosis

Lactic acidosis has been reported with the use of AKLID.

Patients who develop signs and symptoms of metabolic acidosis, including recurrent nausea or vomiting, abdominal pain, a low bicarbonate level or hyperventilation while receiving AKLID, should receive immediate medical attention.

Mitochondrial dysfunction

Linezolid inhibits mitochondrial protein synthesis. Adverse events, such as lactic acidosis, anaemia and neuropathy (optic and peripheral), may occur as a result of this inhibition. These events are more common when AKLID is used longer than 28 days.

Convulsions

Convulsions have been reported in patients treated with AKLID. Patients with a history of seizures or presenting with seizure risk factors, may be predisposed to having convulsions when receiving AKLID. Patients should be advised to inform their medical practitioner if they have a history of seizures.

Porphyria

Caution is advised in patients with porphyria, as AKLID is possibly porphyrinogenic.

Use with tyramine-rich foods

Patients should be advised against consuming tyramine-rich foods (see INTERACTIONS).

Other

The safety and effectiveness of AKLID when taken for periods longer than 28 days have not been established. AKLID has not been studied in patients with untreated hyperthyroidism.

Special populations

Caution is advised when used in patients with severe renal and/or hepatic insufficiency.

Lactose

AKLID film coated tablets contain lactose. Patients who are lactose intolerant or have rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, should not take AKLID film coated tablets.

Effects on ability to drive and use machinery

AKLID can cause side effects, such as dizziness, hypotension or blurred vision. Caution is advised before driving a vehicle or operating machinery, until the effects of AKLID are known.

INTERACTIONS

• AKLID is a monoamine oxidase inhibitor (MAOI) and has the potential to interact with adrenergic and serotonergic agents. AKLID is contraindicated in patients treated with MAO inhibitors, or within two weeks of taking them (see CONTRAINDICATIONS). Enhanced pressor activity has been reported in patients taking AKLID in combination with phenylpropanolamine or pseudoephedrine and doses of compounds such as dopamine or adrenaline should be reduced.

• Tyramine containing foods (e.g. matured cheese, yeast extracts, undistilled alcoholic beverages and fermented soybean products such as soy sauce) may cause a significant pressor response if consumed concurrently with AKLID.

• Serotonin syndrome has been reported when AKLID is used concurrently with serotonin reuptake inhibitors (antidepressants) and dextromethorphan (cough suppressant) (see CONTRAINDICATIONS

and WARNINGS AND SPECIAL PRECAUTIONS).

• The use of AKLID with bone marrow suppressants may increase the thrombocytopenic and leucopenic effects of these medicines and weekly blood counts and monitoring is recommended.

• Concomitant use of AKLID with opioid analgesics (pethidine) may result in coma and respiratory depression (see CONTRAINDICATIONS).

• Medicine causing induction of hepatic enzymes (e.g. rifampicin) may cause decreases in AKLID exposure.

PREGNANCY AND LACTATION

The use of AKLID during pregnancy and lactation is contraindicated (see CONTRAINDICATIONS).

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

AKLID may be taken with or without food.

The recommended dosage for AKLID is described below:

Adults and adolescents (12 years and older):

Infections (including those associated with concurrent bacteraemia)	**Twice daily dosage**	**Duration of treatment**

Community acquired pneumonia, including concurrent bacteraemia	600 mg orally	10 – 14 days
Nosocomial pneumonia, including concurrent bacteraemia		
Skin and soft tissue infections, including concurrent bacteraemia	600 mg orally	
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg orally	14 – 28 days

Elderly patients:

No dose adjustment of **AKLID** is necessary.

Patients with impaired renal function:

There is no evidence of AKLID parent substance accumulation in patients with any degree of renal insufficiency.

Patients with mild to moderate renal insufficiency i.e. creatine clearance (CLcR) > 30 ml/min:

No dose adjustment is necessary.

Patients with severe renal insufficiency i.e. CLcR ≤ 30 ml/min:

Caution is advised when used in patients with severe renal insufficiency. Dosage should not be reduced in these patients. However, there is evidence that the primary metabolites of AKLID accumulate in patients with severe renal insufficiency. The clinical significance of this has not been established.

AKLID should be taken after haemodialysis in patients receiving such treatment.

Patients with impaired hepatic function:

Caution is advised when used in patients with severe hepatic function impairment.

SIDE EFFECTS

Infections and infestations

Frequent: Pseudomembranous colitis, oral candidiasis, vaginal candidiasis, candidiasis, fungal infections

Blood and the lymphatic system disorders

Frequent: Myelosuppresion, anaemia, leucopenia, pancytopenia and thrombocytopenia. Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.

Less frequent: Eosinophilia and neutropenia. Increased reticulocyte count. Decreased neutrophils.

Immune system disorders

Less frequent: Hypersensitivity reactions, bullous skin eruptions including Stevens-Johnson syndrome.

Metabolism and nutrition disorders

Less frequent: Lactic acidosis, increased serum creatinine phosphokinase and hyperglycaemia.

Psychiatric disorders

Frequent: Insomnia.

Nervous system disorders

Frequent: Headache, metallic taste.

Less frequent: Hypaesthesia, paraesthesia, peripheral neuropathy, convulsions and serotonin syndrome (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

Eye disorders

Less frequent: Optic neuropathy, blurred vision and loss of vision, visual field defect (see WARNINGS AND SPECIAL PRECAUTIONS) and change in colour vision.

Ear and labyrinth disorders

Less frequent: Tinnitus.

Vascular disorders

Less frequent: Dizziness, hypertension and hypotension.

Gastrointestinal disorders

Frequent: Diarrhoea, pseudomembranous colitis, nausea, vomiting, constipation, metallic taste, oral candidiasis, abdominal pain and cramps or distension.

Less frequent: Dry mouth, dyspepsia, gastritis, increased thirst, pancreatitis and tongue or teeth discolouration.

Skin and subcutaneous tissue disorders

Less frequent: Dermatitis, diaphoresis, pruritus, rash and urticaria.

Renal and urinary disorders

Less frequent: Polyuria.

Reproductive system and breast disorders

Less frequent: Vulvovaginal disorder and vaginitis.

General disorders and administrative site conditions

Frequent: Fever.

Less frequent: Fatigue and chills, injection site pain, phlebitis or thrombophlebitis, localised pain.

Investigations

Frequent: Increased bilirubin, AST, ALT, LDH, alkaline phosphatase, BUN, creatine kinase, lipase, amylase or non-fasting glucose. Decreased total protein, albumin, sodium, calcium. Increased or decreased potassium or bicarbonate.

Less frequent: Increased creatinine, sodium, calcium. Decreased non-fasting glucose. Increased or decreased chloride

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See SIDE EFFECTS.

Treatment is supportive with maintenance of glomerular filtration. Approximately 30% of linezolid is removed by 3 hours of haemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion.

IDENTIFICATION

White, oval biconvex tablets.

PRESENTATION

A cardboard box containing silver aluminium / aluminium blister strips containing 1x6, 2x14 or 3x10 film coated tablets and a package insert, or

A cardboard box containing white PVC/PE/PVDC / silver aluminium foil blister strips, containing 1x9, 1x10, 2x14 or 3x10 film-coated tablets and a package insert, or

A cardboard box containing a white HDPE bottle, with a child resistant screw cap and mounted desiccant containing 10 or 30 film coated tablets and a package insert.

Pack sizes: 6, 9, 10, 28 and 30 film coated tablets.

STORAGE INSTRUCTIONS

Store at or below 30 ºC.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

48/20.1.1/0949

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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