Guidance for the use of Linezolid in the Treatment of Pneumonia and Severe Skin and Soft Tissue Infections

Introduction:

Linezolid is a synthetic antibiotic, which comes from a class of antimicrobials called the oxazolidinones. It has in vitro activity against aerobic Gram positive bacteria and anaerobic micro-organisms. It is not active against infections caused by Gram negative pathogens.

Its mechanism of action involves disruption of bacterial growth by inhibiting protein synthesis. The site of inhibition occurs earlier in the initiation process of protein synthesis so cross-resistance to other protein synthesis inhibitors (clindamycin, aminoglycosides and macrolides) has not yet been reported.

Linezolid should only be prescribed on the advice of a consultant microbiologist.

Contraindications[2]:

- Hypersensitivity to Linezolid or any of its excipients.
- Concomitant use with *or within 2 weeks of stopping* any drug, which inhibits monoamine oxidases A or B (for example; the monoamine oxidase inhibitor antidepressants [Phenelzine, Isocarboxazid, Moclobemide] and the anti-Parkinson's Disease drugs [Rasagiline, Selegiline]).
- Uncontrolled hypertension, Phaeochromocytoma (unless close monitoring of blood pressure is available).
- Carcinoid.
- Thyrotoxicosis.
- Bipolar disorder, Schizoaffective disorder and Acute confusional states.
- With any of the following medications:
    - Serotonin re-uptake inhibitors and tricyclic antidepressants
    - Serotonin 5-HT_1 agonists (Sumatriptan, etc)
    - Directly and indirectly acting sympathomimetic agents (including adrenergic bronchodilators, Pseudoephedrine and phenylpropanolamine)
    - Vasopressors (adrenaline, noradrenaline)
    - Dopaminergic agents (Dopamine, Dobutamine and some anti-Parkinson's Disease agents)
    - Pethidine
    - Buspirone
- Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breast-feeding should be discontinued prior to and throughout administration.

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Special warnings and precautions for use[2, 3]:

- Myelosupression (anaemia, thrombocytopenia, leucopenia, pancytopenia)
  - Dependent on the duration of treatment.
  - Blood dyscrasias are more common in elderly patients than in younger patients.
  - Thrombocytopenia may occur more commonly in patients with severe renal insufficiency. **The decision to treat should only occur if close monitoring of Full blood counts (FBCs) is available in such cases.**
  - Monitor FBCs (including haemoglobin, platelets, and total and differentiated leucocytes) ***every week of treatment***, regardless of baseline levels.
  - Close monitoring of blood counts is necessary if patients have existing blood disorders, are receiving medication that may affect FBCs, have renal impairment or who receive more than 10-14 days of treatment.
  - Stop therapy if significant myelosupression occurs. If required to continue, ensure very close monitoring of FBCs and manage deficiencies as necessary. Complete recovery has been reported on stopping therapy.
- Antibiotic-associated diarrhoea and colitis
  - Has been reported in association with the use of Linezolid and may range in severity from mild diarrhoea to fatal colitis.
  - Stop therapy if symptoms are suspected to be antibiotic-induced and adequate therapeutic measures should be initiated immediately.
  - Avoid the concomitant use of medications that inhibit peristalsis (i.e. opioid analgesics, loperamide) if there are confirmed cases of antibiotic-associated diarrhoea or colitis.
  - Concomitant use of Proton-pump inhibitors (omeprazole, etc) should be avoided to reduce the risk of development of antibiotic-associated diarrhoea, colitis and *Clostridium-difficile*-associated diarrhoea.
- Lactic acidosis
  - Immediate medical attention should be sought if signs and symptoms of metabolic acidosis (recurrent nausea or vomiting, abdominal pain, hyperventilation or low bicarbonate levels) occur.
  - Continuation of therapy should be after a potential risk versus benefit assessment.
- Mitochondrial Dysfunction
  - Linezolid inhibits mitochondrial protein synthesis. Adverse events e.g. lactic acidosis, anaemia and neuropathy (optic and peripheral) may occur as a result of this inhibition.
  - These events are more common when the drug is used for longer than 28 days.

- Serotonin syndrome
    - Most common if used concomitantly with serotonergic agents (i.e. antidepressants such as the SSRIs).

    - Avoid use with serotonergic agents unless absolutely necessary. Monitor patient closely for symptoms of Serotonin Syndrome (rapid onset of symptoms of tachycardia, hypertension, sweating, dilated pupils, hyperthermia, agitation, seizures, hyperpyrexia, hyperreflexia, and cognitive dysfunction).

    - If signs or symptoms occur, physicians should consider discontinuing either one or both agents (however if concomitant serotonergic agent is discontinued, withdrawal symptoms may occur).

- Peripheral and optic neuropathy
    - More common if duration of therapy exceeds 28 days.

    - Advise patients to immediately report any visual changes (changes in visual acuity, colour vision, blurred vision, visual field defects). Refer to an ophthalmologist if this occurs. Any patients requiring more than 28 days treatment should have their visual function checked regularly.

    - Neuropathies are more common if patients are concomitantly using anti-tuberculosis medications.

    - The decision to continue therapy in such cases should be after assessment of risks versus the benefits of therapy.

- Convulsions
    - Most cases involve patients with either risk factors for or a history of seizures.

    - Caution must be exercised if used in such patients.

- Mono-amine Oxidase inhibitors
    - Linezolid is a reversible, non-selective monoamine oxidase (MAO) inhibitor (but does not exhibit any antidepressant activity at the doses used for antibacterial therapy).

    - Use of Linezolid with any other medications or conditions that may cause MAO inhibition is contraindicated due to a lack of experience with its concomitant use.

- Special populations
    - Linezolid should be used with special caution in patients with severe renal insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk.

    - It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk.

- Impairment of fertility
    - Linezolid reversibly decreased fertility and induced abnormal sperm morphology in adult male rats at exposure levels approximately equal to those expected in humans; possible effects of linezolid on the human male reproductive system are not known.

Drug Interactions[4]

- Mono-amine Oxidase Inhibitors (avoid use with or within two weeks of stopping an MAOI)
- Tyramine-rich foods (e.g. mature cheese, yeast extracts, un-distilled alcoholic beverages and fermented soya bean products such as soy sauce).
- Vasopressors (adrenaline, noradrenaline)
- Dopaminergic agents (i.e. Dopamine, Dobutamine and some anti-Parkinson's Disease agents)
- Serotonergic agents (Tramadol, antidepressants; SSRIs, SNRIs and TCAs)
- Rifampicin (risk of treatment failure as rifampicin reduces the plasma concentration of Linezolid)
- Serotonin 5-HT_1 agonists (Sumatriptan, etc)
- Bupropion (hypertension)
- Clarithromycin (increased exposure to Linezolid)
- Buspirone (risk of serotonin syndrome)
- Nasal decongestants (pseudoephedrine)
- Pethidine (risk of serotonin syndrome)
- Lithium (risk of Serotonin syndrome and elevated serum Lithium)

Dosage, administration and treatment duration[2, 3]:

Duration of therapy depends on the type of infection, its site and severity; however, treatment lasting longer than 28 days increases the risk of adverse effects. Some patients may require shorter courses than recommended below.

Infection type	Dosage (IV/PO)*	Duration of treatment	
Hospital-acquired pneumonia	600mg BD	10-14 consecutive days Maximum 28 days	No dose adjustment is necessary in renal and hepatic impairment.
Community-acquired pneumonia			
Complicated skin and soft tissue infections			

*The oral preparations (tablets and suspension) have 100% bioavailability thus no dose adjustment is necessary when switching between IV and oral formulations.

Excipients[2]:

The tablet core contains the following: Microcrystalline cellulose, Silica colloidal anhydrous, Sodium starch glycollate type A, Hydroxypropylcellulose, Magnesium stearate.

The film coat contains the following: Hypromellose (E464), Titanium dioxide (E171), Macrogol (E1521)

Monitoring:

Monitoring parameter	Monitoring period
FBC	Weekly for each week of treatment
Vision	Checked regularly if using long term
Blood pressure	If uncontrolled BP and necessary to treat
Liver and Renal function	Unless pre-existing impairment is present

Adverse effects[2, 3]:

Common

- Headache
- Diarrhoea
- Nausea and vomiting
- Oral and vaginal candidiasis
- Metallic taste
- Abnormal LFTs
- Abnormal FBCs
- Electrolyte disturbances

Uncommon

- Visual defects
- Blurred vision
- Tinnitus
- Hypertension, phlebitis, thrombophlebitis
- Leucopenia, neutropenia, thrombocytopenia, eosinophilia
- Insomnia
- Paraesthesia
- Hypoaesthesia
- Dizziness
- Vaginitis
- Pancreatitis
- Gastritis
- Dyspepsia
- Loose stools
- Stomatitis
- Glossitis
- Abdominal pain
- Constipation
- Dry mouth
- Increased serum Creatinine
- Polyuria
- Urticaria
- Rash
- Vulvovaginal disorder
- Chills, fever, fatigue

Rare

- Renal failure
- Arrhythmia (Tachycardia)
- Transient ischemic attack

Pregnancy and Lactation:

Animal studies show the potential for reproductive toxicity; therefore, Linezolid should be avoided unless the benefits of using it outweigh its risks.

There is a potential for Linezolid to pass in to the breast milk, thus it is recommended to avoid breastfeeding during treatment.

Immediate advice and support:

Contact Details	Telephone No	Fax No	Email
Medicines Information BHNFT	01226 432857	01226 434431	Gilliansmith2@nhs.net
Antimicrobial Pharmacist	01226 433070	01226 434431	
Dr J. Rao	01226 432749		
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References:

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This prescribing guideline was ratified by the Area Prescribing Committee on 14th October 2020