

PROFESSIONAL INFORMATION

SCHEDULING STATUS: **[S4]**

PROPRIETARY NAME AND DOSAGE FORM
LINOBACT® FC Film-coated tablets

COMPOSITION
Each LINOBACT FC tablet contains 600 mg linezolid.

Inactive ingredients:
Core: Cellulose (microcrystalline), lactose monohydrate, magnesium stearate, poloxamer 407, povidone K30, silica (colloidal anhydrous), sodium starch glycolate, talc.
Coating: Blue printing ink (proprietary mixture containing FD&C Blue No. 1 as colourant), Opadry white YS-1-18202-A (containing hypromellose, macrogol and titanium dioxide).
Contains sugar (25.20 mg lactose monohydrate per tablet).

PHARMACOLOGICAL CLASSIFICATION
A20.1.1 Broad band medium spectrum antibiotics

PHARMACOLOGICAL ACTION
Pharmacodynamic properties

Linezolid is a synthetic antibiotic that belongs to the oxazolidinone class of antibiotics. It is bacteriostatic against enterococci and staphylococci and bactericidal against streptococci. Linezolid is not active against most Gram-negative aerobic or anaerobic bacteria. (see **INDICATIONS**).

Linezolid has *in vitro* activity against aerobic Gram-positive bacteria. *In vitro* susceptibility does not necessarily imply clinical bactericidal activity. Linezolid selectively inhibits bacterial protein synthesis through binding to sites on the bacterial ribosome and prevents the formation of a functional 70S initiation complex, which is a necessary component of the translation process.

Resistant organisms:

Haemophilus influenzae
Enterobacteriaceae
Neisseria species
Pseudomonas species

Resistance:

Resistance to linezolid develops slowly via multiple step mutation in 23S ribosomal RNA and has been reported to occur at frequencies of less than 1×10^{-6} to 1×10^{-11} . Cross-resistance between linezolid and the following molecules is not expected: aminoglycosides, beta-lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifamycins, streptogramins, tetracyclines and chloramphenicol.

Pharmacokinetic properties

Absorption:
Maximum plasma concentrations are reached within 2 hours of dosing and absolute bioavailability is approximately 100 %. Linezolid is well absorbed, with or without food.

Distribution:

The volume of distribution at steady-state is about 40 to 50 litres in healthy adults. Plasma protein binding is about 31 %.

Metabolism:

Linezolid is primarily metabolised by oxidation of the morpholine ring resulting mainly in the formation of two inactive open-ring carboxylic acid derivatives; the aminoethoxyacetic acid metabolite (A) and the hydroxyethyl glycine metabolite (B). The hydroxyethyl glycine metabolite (B) is the predominant human metabolite and is reportedly formed by a non-enzymatic process. The aminoethoxyacetic acid metabolite (A) is less abundant. Linezolid is not detectably metabolised by cytochrome P450 (CYP) isoenzymes *in vitro* and it does not inhibit the activities of clinically significant human CYP isoenzymes (IA2, 2C9, 2C19, 2D6, 2E1, 3A4). Linezolid does not significantly induce major cytochrome P450 isoenzymes in rats and does not induce human CYP2C9.

Elimination:

Under steady-state conditions, linezolid is primarily excreted in the urine as metabolite B (40 %) parent compound (30 - 35 %) and metabolite A (10 %). The parent compound has a mean elimination half-life of 5-7 hours. Non-renal clearance accounts for approximately 65 % of the total clearance of linezolid.

Special populations

Elderly:

The pharmacokinetics of linezolid is not significantly altered in elderly patients aged 65 and over.

Renal insufficiency:

No dose adjustment is necessary in patients with either mild, moderate or severe renal insufficiency, as linezolid clearance is independent of creatinine clearance.

Primary metabolites of linezolid can accumulate in patients with severe renal insufficiency (i.e. $CL_{CR} < 30$ ml/min) but the clinical significance has not yet been established. As approximately 30 % of dose is removed during 3 hours of haemodialysis (beginning 3 hours after administration), LINOBACT FC should be given after dialysis in patients receiving such treatment.

Hepatic insufficiency:

The pharmacokinetics of linezolid are not altered in patients with mild to moderate hepatic insufficiency and a dose adjustment with LINOBACT FC is therefore not required for these patients. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency have not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

Children:

With increasing age of paediatric patients, the clearance of linezolid gradually decreases; by adolescence the mean clearance values approach those observed in adults. There is wider inter-subject variability in linezolid clearance and systemic medicine exposure (AUC) across all paediatric age groups, compared with adults. LINOBACT FC are not indicated for children under 12 years of age (see **DOSE AND DIRECTIONS FOR USE**).

INDICATIONS

LINOBACT FC is indicated for the treatment of patients with the following infections, which are caused by susceptible strains of micro-organisms:

- **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.
- **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).
- **Complicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. 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), *Streptococcus pyogenes*.

**MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as penicillin-resistant *Streptococcus pneumoniae*, and are strains resistant to two or more of the following antibiotics: penicillin, second generation cephalosporins, macrolides, tetracycline and trimethoprim/sulfamethoxazole.

CONTRAINDICATIONS

LINOBACT FC tablets are contraindicated for use:

- in patients who have known hypersensitivity to linezolid or any of the excipients in the formulation (see **COMPOSITION**);
- in patients taking any medicine which inhibits monoamine oxidase A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks of taking any of these medicines.

WARNINGS AND SPECIAL PRECAUTIONS

Pseudomembranous colitis

Myelosuppression may occur. Anaemia, pure red blood cell aplasia, leukopenia, pancytopenia and thrombocytopenia have been reported in patients receiving LINOBACT FC (see **SIDE EFFECTS**). Patients particularly at risk are those who have received LINOBACT FC for more than 10 or 14 days, who are receiving other bone marrow suppressant medicines, patients with severe renal insufficiency, or who have pre-existing myelosuppression. The risk/benefit should be thoroughly considered in patients with worsening myelosuppression. Discontinuation of therapy with linezolid should be considered in patients who develop, or have worsening, myelosuppression.

Monitoring of full blood counts should be done for patients exposed to an increased risk for bleeding, who have pre-existing myelosuppression, who received concomitant medications which may decrease haemoglobin levels or platelet count or platelet function, or who have received LINOBACT FC for longer than 2 weeks.

Antibacterial spectrum

LINOBACT FC has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections (see **Pharmacodynamic properties** and **INDICATIONS**). Patients with mixed (Gram-negative and Gram-positive) infections are at a higher risk of mortality when LINOBACT FC is given as monotherapy; LINOBACT FC must therefore be used with appropriate antibacterial cover for Gram-negative organisms in such patients. LINOBACT FC should be used with special caution in patients exposed to a high risk for life-threatening systemic infections, such as those with infections related to central venous catheters in intensive care units. LINOBACT FC is not intended for the treatment of patients with catheter-related infections of the blood stream.

Serotonin syndrome

Serotonin syndrome has been reported with concomitant administration of linezolid and serotonergic agents (such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and 5-HT₂ receptor agonists). Doctors should be alert to the possibility of signs and symptoms of serotonin syndrome (e.g. hyperpyrexia, incoordination and cognitive dysfunction) in patients receiving such concomitant therapy with LINOBACT FC (see **INTERACTIONS, "Serotonergic Interactions"**). If signs or symptoms occur, doctors should consider discontinuing either one or both agents. Should the concomitant serotonergic agent be withdrawn, discontinuation symptoms may occur.

Peripheral and optic neuropathy

Peripheral and optic neuropathy and optic neuritis, sometimes progressing to loss of vision have been reported with LINOBACT FC (see **SIDE EFFECTS**). These side effects mainly occurred in patients treated for longer than the maximum recommended duration of 28 days (see **Treatment period**). The continued use of LINOBACT FC should be weighed against the potential risks. If a patient is taking LINOBACT FC for longer than the recommended 28 days, their visual function should be regularly monitored. There may be an increased risk of neuropathies when LINOBACT FC is used in patients currently taking, or who have recently taken, antibacterial medicines for the treatment of tuberculosis (see **INTERACTIONS**).

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. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary.

Convulsions

Convulsions may occur in patients treated with LINOBACT FC (see **SIDE EFFECTS**), particularly in patients with a history of convulsions, or risk factors for convulsions.

Resistance

- There have been reports of linezolid resistance in:
 - enterococci
 - staphylococci, such as methicillin-resistant *Staphylococcus aureus*, *S. auricularis* and *S. epidermidis*.

Treatment period

The safety and effectiveness of LINOBACT FC when administered for periods longer than 28 days have not been established. See also **Mitochondrial dysfunction** above.

Patient populations

Underlying clinical conditions

LINOBACT FC has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, bipolar depression, schizophrenia disorder or acute confusional states. If LINOBACT FC is used at all in these patients, they should be carefully monitored for potential increases in blood pressure.

Porphyria

LINOBACT FC is possibly porphyrogenic and should therefore only be used when no safer alternative is available and precautions should be considered in vulnerable patients.

Renal impairment

LINOBACT FC should be used with special care in patients with severe renal impairment and only when the expected benefit is considered to exceed the theoretical risk.

Hepatic impairment

It is recommended that LINOBACT FC should only be considered for treatment in patients with severe hepatic insufficiency only when the expected benefit is considered to exceed the theoretical risk.

Effects on ability to drive and use machines:

Patients should be informed not to drive or handle machinery or tools if they experience dizziness or visual impairment (see **SIDE EFFECTS**).

Lactose

LINOBACT FC tablets contain lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take LINOBACT FC. LINOBACT FC may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS

LINOBACT FC is contraindicated in patients treated with monoamine oxidase inhibitors or within two weeks of taking such a medicine (see **CONTRAINDICATIONS**).

LINOBACT FC is a reversible, non-selective monoamine oxidase inhibitor (MAOI). It produces a mild, reversible inhibition of the pressor responses induced by pseudoephedrine and phenylephrine hydrochloride. The potential for interaction with sympathomimetic or adrenergic agents should therefore be considered (see **WARNINGS AND SPECIAL PRECAUTIONS**). Doses of compounds, such as dopamine or epinephrine (adrenalin), should be titrated to achieve the desired response.

Cytochrome P450 interactions

LINOBACT FC is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not induce or inhibit the activities of clinically significant human CYP isoenzymes (IA2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-induced medicine interactions are expected. Phenytoin, which is a CYP2C9 substrate, may be given with LINOBACT FC without changes in dosage regimen. Also, no interactions have been observed with either aztreonam or gentamicin.

Tyramine-rich foods

Large amounts of food and beverages with high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce) should be avoided to prevent a pressor response.

Serotonergic interactions

Serotonin syndrome, associated with the simultaneous administration of LINOBACT FC and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) has been reported (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**). Although LINOBACT FC has the potential for interaction with serotonergic agents, no serotonergic effects were observed in subjects receiving linezolid and dextromethorphan.

Opioid analgesics

Pethidine should not be given to patients receiving MAO inhibitors (including LINOBACT FC) or within 14 days of their discontinuation. Very severe reactions, including coma, severe respiratory depression, cyanosis and hypotension may occur.

Rifampicin

Concomitant administration of rifampicin with LINOBACT FC may cause a decrease of about 20 % in linezolid C_{max} and a decrease of about 30 % in linezolid AUC. The mechanism of this interaction and the clinical significance thereof is not known.

HUMAN REPRODUCTION

Pregnancy and lactation

The use of LINOBACT FC tablets in pregnancy and lactation is contraindicated, as safety has not been demonstrated. LINOBACT FC may be secreted into breast milk.

Fertility

Linezolid, as in LINOBACT FC, reversibly decreased fertility and induced abnormal sperm morphology in animals. The possible effect on the human male reproductive system has not been established.

DOSE AND DIRECTIONS FOR USE

LINOBACT FC tablets may be used as initial therapy. Patients who commence treatment on the parenteral solution may be switched to the tablet formulation when clinically indicated. No dose adjustment is required, as LINOBACT FC has an oral bioavailability of approximately 100 %. LINOBACT FC tablets may be taken with or without food. The recommended dosage schedule for LINOBACT FC is as follows:

Adult and adolescent (12 years and older) patients:

Infections (including those associated with concurrent bacteraemia)	Dosage and route of administration	Duration of treatment
Community-acquired pneumonia, including concurrent bacteraemia	600 mg orally every 12 hours	10 - 14 consecutive days
Nosocomial pneumonia, including concurrent bacteraemia	600 mg orally every 12 hours, depending on clinical severity	14 - 28 consecutive days
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg orally every 12 hours	14 - 28 consecutive days

- For patients younger than 12 years, the recommended dose is 10 mg/kg every 8 hours. This product is not suitable for use in children, as LINOBACT FC cannot be divided; please refer to the dosage recommendations in professional information of infusion or oral suspension formulations of linezolid.

Elderly patients:

No dose adjustment is necessary.

Patients with renal impairment:

- Patients with mild to moderate renal insufficiency, i.e. CL_{CR} (creatinine clearance) > 30 ml/min.
- No dosage adjustment is required.
- Patients with serious renal impairment (i.e. $CL_{CR} < 30$ ml/min): Dosage should not be reduced in these patients. However, evidence indicates that the primary metabolites of LINOBACT FC accumulate in patients with severe renal insufficiency. The clinical significance has not been established. LINOBACT FC should only be used with special care in these patients, when the expected benefit is considered to exceed the theoretical risk.

• Haemodialysis: LINOBACT FC should be given after dialysis in patients receiving such treatment.

Patients with hepatic impairment:

No dose adjustment is required.

SIDE EFFECTS

Infections and infestations:

Frequent: Oral and vaginal moniliasis, moniliasis or fungal infection.
Less frequent: Antibiotic associated colitis, *Clostridium difficile* associated diarrhoea (CDAD), pseudomembranous colitis (may be fatal); see **WARNINGS AND SPECIAL PRECAUTIONS**, vaginitis.

Blood and the lymphatic system disorders:

Less frequent: Myelosuppression* with anaemia*, eosinophilia, leukopenia*, neutropenia, thrombocytopenia*, pancytopenia*, sideroblastic anaemia*.

Immune system disorders:

Frequency not known: Hypersensitivity reactions, anaphylaxis, angioedema, bullous skin disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Metabolism and nutrition disorders:

Less frequent: Increased serum creatine phosphokinase, hyperglycaemia, lactic acidosis*, hyponatraemia.

Psychiatric disorders:

Frequent: Insomnia.

Nervous system disorders:

Frequent: Headache, taste alterations, metallic taste.
Less frequent: Dizziness, hypoesthesia, paraesthesia, peripheral neuropathy*, convulsions*, serotonin syndrome**.

Eye disorders:

Less frequent: Blurred vision*, optical neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*, changes in visual field defect*.

Ear and labyrinth disorders:

Less frequent: Tinnitus.

Cardiac disorders:

Less frequent: Dysrhythmia (tachycardia).

Vascular disorders:

Less frequent: Hypertension, hypotension, phlebitis, thrombophlebitis, transient ischaemic attacks.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, abdominal pain, cramps or distension.
Less frequent: Constipation, dry mouth, dyspepsia, gastritis, pancreatitis, stomatitis, tongue discoloration or disorder, localised or general abdominal pain, glossitis, loose stools.

Hepatobiliary disorders:

Frequent: Abnormal liver function tests (see **Investigations** below).

Skin and subcutaneous tissue disorders:

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

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Superficial tooth discoloration.

Renal and urinary disorders:

Less frequent: Polyuria, increased creatinine, renal failure.

Reproductive system and breast disorders:

Less frequent: Vulvovaginal disorder.

General disorders and administration site conditions:

Less frequent: Chills, fatigue, fever, increased thirst.

Investigations:

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

Blood: Increased neutrophils or eosinophils, decreased haemoglobin, haematocrit or red blood cell count, increased or decreased platelet or white blood cell counts.

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

Blood: Increased reticulocyte count, decreased neutrophils.

See **WARNINGS AND SPECIAL PRECAUTIONS.

***See **CONTRAINDICATIONS** and **INTERACTIONS**.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In the event of overdose, supportive care is advised together with maintenance of glomerular filtration. Approximately 30 % of LINOBACT FC dose is removed during 3 hours of haemodialysis, but no data are available for the removal of LINOBACT FC by peritoneal dialysis or haemoperfusion.

IDENTIFICATION

LINOBACT FC tablets are white, oval, biconvex, film-coated tablets, with "600" printed on one side with blue ink.

PRESENTATION

- Cardboard box containing PA/ALL/PVC - Aluminium foil (silver) blisters with 10 or 30 film-coated tablets.
- Cardboard box containing PVC/PE/PVDC (white) - Aluminium foil (silver) blisters with 10 or 30 film-coated tablets.
- Cardboard box containing one white opaque HDPE container (bottle) with white polypropylene child resistant screw cap and white polyethylene mounted desiccant containing silica gel, with 10 or 30 film-coated tablets and an instruction leaflet.

All pack sizes may not necessarily be marketed at one time.

STORAGE INSTRUCTIONS

Store at or below 25 °C in the original packaging. Keep bottle or blister strips in the cartons until required for use. Keep the bottles well-closed. Keep out of reach of children.

REGISTRATION NUMBER

49/20.1.1/0721

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

Astral Pharma (Pty) Ltd
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PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: **[S4]**

PROPRIETARY NAME AND DOSAGE FORM
LINOBACT® FC Film-coated tablet

Read all of this leaflet carefully before you start taking LINOBACT FC

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- LINOBACT FC has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT LINOBACT FC CONTAINS

Each LINOBACT FC tablet contains 600 mg linezolid.

Inactive ingredients:

Core: Cellulose (microcrystalline), lactose monohydrate, magnesium stearate, poloxamer 407, povidone K30, silica (colloidal anhydrous), sodium starch glycolate, talc.
Coating: Blue printing ink (proprietary mixture containing FD&C Blue No. 1 as colourant), Opadry white YS-1-18202-A (containing hypromellose, macrogol and titanium dioxide).
Contains sugar (25.20 mg lactose monohydrate per tablet).

WHAT LINOBACT FC IS USED FOR

The active ingredient, linezolid, is an antibiotic of the so-called oxazolidinones group. It either stops the growth of certain types of bacteria (germs) or limits the growth of other types of bacteria that cause infections.

LINOBACT FC tablets may be used for various infections.

BEFORE YOU TAKE LINOBACT FC

Do not take LINOBACT FC:

- if you are hypersensitive (allergic) to linezolid or any of the other ingredients of LINOBACT FC (see **WHAT LINOBACT FC CONTAINS**);
- if you are treated with monoamine oxidase inhibitors (MAOIs), or within two weeks of taking such a medicine. MAOIs (such as phenelzine, selegiline, moclobemide) may be used to treat depression or Parkinson's disease.

Take special care with LINOBACT FC:

While you are taking LINOBACT FC, your doctor may perform regular blood tests to monitor changes in your blood count (see **POSSIBLE SIDE EFFECTS**). Your doctor will monitor your eyesight if you take LINOBACT FC for more than 28 days (see **POSSIBLE SIDE EFFECTS**).

Tell your doctor:

- if you have diarrhoea. LINOBACT FC may cause serious, life-threatening diarrhoea and inflammation of your bowels (see **POSSIBLE SIDE EFFECTS**);
- if you develop recurrent nausea or vomiting, abdominal pain or rapid treatment. You may have a serious metabolic condition and need immediate medical treatment (see **POSSIBLE SIDE EFFECTS**);
- if you develop problems with or if your field of vision becomes restricted (see **POSSIBLE SIDE EFFECTS**);
- if you have been told that you have a low blood cell count (bone marrow suppression). Your doctor may want to check you more frequently and may tell you to avoid sick people to prevent infection;
- if you experience agitation, confusion, coma, stiff muscles, trembling, poor coordination and fits while also taking certain antidepressants (see **Taking other medicines with LINOBACT FC**);
- if you have a history of seizures ("fits");
- if you have high blood pressure and also tell your doctor what medicines you are taking for this (see **Taking other medicines with LINOBACT FC**);</

PROFESIONELE INLIGTING

SCHEDULESTATUS: [**S4**]

EIENDOMSNAAM EN DOSEERVORM:
LINOBACT® FC Filmbedekte tablette

SAMESTELLING
Elke LINOBACT FC tablet bevat 600 mg linesolied.

Onaktiewe bestandele:
Kern: Sellulose (mikrokristallyne), laktose monohidraat, magnesiumstearaat, poloksamer 407, povidon K30, silika (kolloïdale watervry), natriumsteyriglykolat, talk.
Bedekking: Blou drukink (mengsel bevat FD&C Blou No. 1 as kleursel), Opadry wit YS-1-18202-A (bevat hipromellose, makrogol en titaandioksied).
Bevat suiker (25,20 mg laktose monohidraat per tablet).

FARMAKOLOGIESE KLASSIFIKASIE

A 20.1.1 Breë en medium spektrum antibiotikum

FARMAKOLOGIESE WERKING

Farmakologiese eienskappe
Linosolied is 'n sintetiese antibiotikum wat aan die oksasolidinoon klas van antibiotika behoort. Dit is bakteriestatiese teenoor enterokokke en staflokkoke en bakteriedodend ten opsigte van streptokokke. Linosolied is nie aktief teenoor die meeste Gram-negatiewe aërobiese of anaërobiese bakterieë (sien **INDIKASIES**). Linosolied besit *in vitro* aktiwiteit teen aërobiese Gram-positiewe bakterieë. In *in vitro* vatbaarheid impliceer nie noodwendig kliniese sensitiwiteit nie. Linosolied inhibeer bakterieë proteïensintese selektief deur binding aan setels op die bakterieële ribosoom en verhoed die vorming van funksionele 70S-inisiasie kompleks wat 'n essensiële komponent van die transkripsie proses uitmaak.

Waarstandige organismes:

Haemophilus influenzae

Enterobacteriaceae

Neisseria spesies

Pseudomonas spesies

Weerstand:

Weerstand teen linesolied ontwikkel stadig deur veelvoudige-stap mutasies in 23S ribosomale rNS en is aangemeld by frekwensies van minder as 1 x 10⁻⁶ to 1 x 10⁻⁸. Geen kruisweerstand tussen linesolied en die volgende medikasie is waagte nie: aminoglikosiede, beta-laktamamide, tetrasiensuurantagoniste, glikopeptiede, linkosamide, kinolone, rifamisien, streptogramiene, middels, foliensuur- en chloramfenikol.

Farmakinetiese eienskappe

Absorpsie

Maksimum plasmakonsentrasies word binne 2 uur na dosering bereik en absolute bioeskikbaarheid is ongeveer 100 %. Linosolied word wel geabsorbeer, met of sonder voedsel.

Verspreiding:

Die volume van verspreiding in die ewewigtoestand is gemiddeld ongeveer 40 to 50 liters in gesonde volwassenes. Plasmaproteïenbinding is ongeveer 31 %.

Metabolisme:

Linosolied word primêr gemetaboliseer deur oksidasie van die morfolin ring wat hoofsaaklik die vorming van twee onaktiewe oop-ring karboksiesuur derivate tot gevolg het; die amino-etoksi-assymsuurmetaboliet (A) en die hidroksi-etielglisienmetaboliet (B). Die hidroksi-etielglisienmetaboliet (B) is die hoof metaboliet wat in die mens voorkom en word na verloop van tyd deur 'n nie-ensiematiese proses gevorm. Die amino-etoksi-assymsuurmetaboliet (A) is minder volgevoel.

Linosolied word nie deur sitochroom P450 (CYP) isoënsieme *in vitro* gemetaboliseer nie en dit inhibeer nie die aktiwiteit van kliniese beduidende menslike CYP isoënsieme nie (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Linosolied veroorsaak geen beduidende interaksie van die hoof sitochroom P450 isoënsieme in rotte, nie- en indiseer nie menslike CYP2C9 nie.

Eliminasie:

In die ewewigtoestand word linesolied primêr in die urine as metaboliet B (40 %) stamgeneesmiddel (30 - 35 %) en metaboliet A (10 %) uitgeskei. Die eliminasië halfleef tyd van die stamgeneesmiddel is gemiddeld ongeveer 5-7 uur. Nie-renale opruiming is vir ongeveer 65 % van die totale opruiming van linesolied verantwoordelik.

Spesiale bevolkingsgroepe

Bejaardes:

In bejaarde pasiënte van 65 en ouer, is die farmakokinetika van linesolied nie-inhiberend verander nie.

Nierontoereikendheid:

Geen dosisaanpassing is nodig in pasiënte met ligte, matige of ernstige nierontoereikendheid nie, omdat linesolied opruiming onafhanklik van kreatinienruiming is. Daar is bewyse dat die primêre metaboliete van linesolied in pasiënte met ernstige nierontoereikendheid oophop (d.i. CL_{cr} < 30 ml/min); die kliniese belang is nog nie vasgestel nie. Aangesien ongeveer 30 % van 'n dosis tydens 3 uur van hemodialise (wat 3 uur na toediening begin word), moet LINOBACT FC in pasiënte wat sulke behandeling ontvang toegedien word.

Lewerontoereikendheid:

In pasiënte met ligte hepatisse ontoereikendheid is die farmakonetika van linesolied nie verander nie. Dosisaanpassing van LINOBACT FC in sulke pasiënte is nie nodig nie. Die farmakokinetika van linesolied in pasiënte met ernstige leverontoereikendheid is nog nie vasgestel nie. Omdat linesolied egtër deur 'n nie-ensiematiese proses gemetaboliseer word, word daar nie verwag dat inkorting van hepatisse proses die metabolisme van hierdie middel sal beïnvloed nie.

Kinders:

Soos die ouderdom van pediatriese pasiënte toeneem, verminder die opruiming van linesolied geleidelik, en met adoloesensie nader die gemiddelde opruimingswaardes dié wat in die volwasse bevolking waargeneem word. Daar kom 'n groter variasie in linesoliedopruiming en sistemiese geneesmiddellootstelling (AOK) oor alle pediatriese ouderdomsgroepe voor, in verskriklike mate. LINOBACT FC word nie aanbeveel vir kinders onder 12 jaar oud nie (sien **DOSIS EN GEBRUIKSAAFWYSINGS**).

INDIKASIES

LINOBACT FC word aangedui vir die behandeling van pasiënte met die volgende infeksies wat deur vatbare stamme van die aangewese mikroorganismes veroorsaak word:

- Vankomisien-weerstandig** *Enterococcus faecium* infeksies, insluitend gevalle met gelyk-tydige bakteriemie.
- Nosokomiale pneumonie** veroorsaak deur *Staphylococcus aureus* (metsillien-vatbare en -weerstandige stamme), of *Streptococcus pneumoniae* (insluitend veelvoudige-geneesmiddelweerstandige *S. pneumoniae* (MDRSP) stamme). Kombinasie terapie kan klinies aangedui word as die gedokumenteerde of vermoedelike patogene Gram-negatiewe organismes insluit.
- Gemeenskaplike pneumonie** veroorsaak deur *Streptococcus pneumoniae* (insluitend veelvoudige-geneesmiddelweerstandige *S. pneumoniae* (MDRSP) stamme), insluitend gevalle met gelyktydige bakteriemie, of *Staphylococcus aureus* (metsillien-vatbare en -weerstandige stamme).
- Gekompliseerde vel en velstruktuurinfeksies veroorsaak deur** *Staphylococcus aureus* (metsillien-vatbare en -weerstandige stamme), *Streptococcus pyogenes*, of *Streptococcus agalactiae*. Kombinasie terapie mag klinies aangedui word indien die gedokumenteerde of vermoede patogene Gram-negatiewe organismes insluit.
- Ongekompliseerde vel- en velstruktuurinfeksies** veroorsaak deur *Staphylococcus aureus* (metsillien-vatbare en -weerstandige stamme), *Streptococcus pyogenes*. *MDRSP, Veelvoudige-geneesmiddelweerstandige *Streptococcus pneumoniae* insluitende isolate voorheen bekend as pensillienweerstandige *Streptococcus pneumoniae*, en is stamme wat weerstandig is vir twee of meer van die volgende antibiotikums: pensillien, tweede generasie fepalosporiene, makroliede, tetrasielien en trimetoprim/sulfametoksasool.

KONTRAINDIKASIES

LINOBACT FC tablette word teenaangedui vir gebruik:

- in pasiënte wat bekende hipersensitiewiteit teenoor linesolied of enigeen van die ander bestandele in die formulering het (sien **SAMESTELLING**);

- in pasiënte wat enige medikasie neem wat monoamienoksidases A of B (bv. fenelseen, isokarboksasied, selegien, moklobemied) inhibeer of binne twee weke na die inname van so 'n medisinale produk.

WAARSKUWINGS EN SPESIALE VOORSORGMATREELS

Pseudomonasbræuse kolitis

Superinfeksies: Behandeling met LINOBACT FC verander die normale flora van die kolon wat tot oormatige groei van onvatbare organismes soos *Candida* en *Clostridium difficile* mag lei. Antibiotika-geassosieerde diarree (AAD), *Clostridium difficile* – geassosieerde diarree (CDD) en pseudomonasbræuse kolitis is met linesolied (watsef in LINOBACT FC aangemeld en mag in erns van ligte diarree, tot noodeltlike colitis, angetref. Dit is dus belangrik om hierdie diagnose te oorweeg by pasiënte wat na toediening van LINOBACT FC met diarree presenter. Indien superinfeksie gedurende terapie sou voorkom, moet geskikte maatreëls toegees word. Die risiko/voordeel moet deeglik oorweeg word by pasiënte met vergering van diarree.

Laktiese asidose

Laktiese asidose is met die gebruik van LINOBACT FC aangemeld. Pasiënte wat tekens en simptome van metaboliese asidose, wat herhaalde naardeh of braking, buikpyn, 'n lae bikarbonaatvlak, of hiperventilasie ontwikkel tervyl LINOBACT FC geneem word, behoort dadelik mediese aandag te kry. Indien laktiese asidose voorkom, behoort die volgehoue gebruik van LINOBACT FC teen die potensieë risiko opgewee te word.

Mitochondriale disfunksie

Linesolied, bevat in LINOBACT FC, inhibeer mitochondriale proteïensintese. Nadelige gebeurnisse, soos laktiese asidose, anemie en neutropenie (optiese en perifere), mag voorkom as gevolg van hierdie inhibisie; voorkoms hiervan is meer algemeen wanneer LINOBACT FC vir langer as 28 dae gebruik word.

Miëlo-nderdrukking

Miëlo-nderdrukking mag voorkom. Anemie, suiver rooibloedseel aplasie, leukopenie, pansitopenie en trombotisopenie is in sommige pasiënte wat LINOBACT FC ontvang het aangemeld. (sien **NEWE-EFFEKTE**). Pasiënte wat LINOBACT FC vir meer as 10 of 14 dae gebruik het, wat ander beuntruogendrukkende medikasie ontvang, pasiënte met ernstige nierversaking, of wat voorafbestaende miëlo-nderdrukking het, is veral riskant. Die risiko/voordeel behoort deeglik oorweeg te word in pasiënte met vergerende miëlo-nderdrukking. Die staking van behandeling met linesolied behoort oorweeg te word by pasiënte wat miëlo-nderdrukking ontwikkel, of wat vergerende miëlo-nderdrukking het. Monitoring van volbloedtellings behoort gedoen te word vir pasiënte wat aan verhoogde risiko van bloeding blootgestel is, wat voorafbestaende miëlo-nderdrukking het, wat gelyktydige medikasies ontvang wat hemoglobiënvakke of plaatjietelling of -funksie mag verminder, of wat LINOBACT FC vir langer as 2 weke ontvang.

Antibakteriale spektrum

LINOBACT FC het geen kliniese aktiwiteit teen Gram-negatiewe patogene nie en word nie vir die behandeling van Gram-negatiewe infeksies aangedui nie (sien **Farmakodinamiese eienskappe** en **INDIKASIES**).

Pasiënte met gemengde Gram-negatiewe en Gram-positiewe infeksies het 'n hoër risiko van mortaliteit wanneer LINOBACT FC as monoterapie toegedien word; LINOBACT FC moet dus saam met gepaste antibakteriese bedekking vir Gam-negatiewe organismes gebruik word vir sulke pasiënte. LINOBACT FC behoort met spesiale versigtigheid gebruik te word by pasiënte wat aan 'n hoër risiko vir lewensbedreigende sistemiese infeksies blootgestel is, soos dié met infeksies wat verwant is aan sentrale venese kateters in intensiewe sorgseenhede. LINOBACT FC is nie goedgekeur vir behandel van pasiënte met kateter-verwante infeksies van die bloedstroom nie.

Serotoniensindroom

Serotoniensindroom is aangemeld met gelyktydige toediening van linesolied en serotonerjiese middels (soos selektiewe serotonien heropname inhibeerders (SSRIs), trisikliese-antidepressante en serotonien 5-HT₂ reseptor agoniste). Dokters behoort bedag te wees op die moontlikheid van tekens en simptome van serotoniensindroom (bv. hiperrefleksie, indokordinasie en kognitiewe disfunksie) in pasiënte wat gelyktydige terapie met LINOBACT FC ontvang, (sien **INTERAKSIES**, **Serotonergiese interaksies**”). Indien tekens of simptome voorkom, behoort dokters die staking van een of beide middels te oorweeg. Sou die gelyktydige serotonerjiese middel onttrek word, mag stakingsimptome voorkom.

Perfore en optiese neuropatie

Perifere en optiese neuropatie en optiese neuritis, wat soms vorder na verlies van sig, is aangemeld by pasiënte wat met LINOBACT FC behandel is. (sien **NEWE EFFEKTE**). Hierdie newe effekte is hoofsaaklik aangetref by pasiënte wat vir langer as die maksimum aanbevole duur, van 28 dae, behandel is. (sien **Duur van behandeling**). Die voorgesette gebruik van LINOBACT FC behoort teen die potensieë risiko's opgewee te word. Indien 'n pasiënt LINOBACT FC vir langer as die aanbevole 28 dae gebruik, behoort hul visuele funksie gereeld gemonitor te word. Daar mag 'n verhoogde risiko van neuropatieë wees wanneer LINOBACT FC gebruik word by pasiënte wat huidigeg antibakteriese medikasie vir die behandeling van tuberkulose neem, of wat dit onlangs geneem het. (sien **INTERAKSIES**).

Pasiënte behoort aangeraai te word om simptome van verswakte sig, soms verandering in visuele skerphed, veranderings in kleurvisie, belemmerde visie of 'n visuele velddefek, aan te meld. Onmiddellike evaluering word in hierdie gevalle aanbeveel, met verwysing na 'n oftalmoloog indien nodig.

Konvulsies

Konvulsies mag voorkom by pasiënte wat behandel word met LINOBACT FC (sien **NEWE EFFEKTE**), veral in pasiënte met 'n geskiedenis van konvulsies, of risikofaktore vir konvulsies.

Weerstand

Linesolied weerstand is al aangemeld in:

- enterokokke
- staflokokke, soos metsillien-weerstandige *Staflokokkus aureus*, *S. auricularis* en *S. epidermidis*.

Duur van behandeling

Die veiligheid en doeltreffendheid van LINOBACT FC is nog nie vasgestel wanneer dit vir langer as 28 dae toegedien word nie. sien ook **Mitochondriale disfunksie** hier bo.

Pasiënt bevolkingsgroepe

Onderliggende kliniese kondisies

LINOBACT FC is nog nie in pasiënte met onbeheerde hipertensie, feochromositoom, karsinoidesindroom, onbeheerde hipertensie, hipotensie, bipolêre depressie, skiso-afektiewe versteuring of akute verwarrende toestande. Indien LINOBACT FC enigins in hierdie pasiënte gebruik word, behoort hulle versigtig gemonitor te word vir potensieë verhogings in bloeddruk.

Portire

LINOBACT FC is moontlik porfiringonee en moet dus slegs gebruik word wanneer daar geen veiliger alternatief beskikbaar is nie; voorsorgmaatreëls behoort getref te word vir kwesbare pasiënte.

Nierversaking

LINOBACT FC behoort met spesiale versigtigheid gebruik te word by pasiënte met ernstige nierontbreikendheid en slegs as daar gedink word dat die verwagte voordeel die toetreesie risiko sal oortref.

Lewer inkorting

Dit word aanbeveel dat LINOBACT FC slegs by pasiënte met ernstige hepatisse ontoereikendheid gebruik moet word as daar gedink word dat die verwagte voordeel die toetreesie risiko sal oortref.

Uitwerking op die vermoë om te bestuur en masjinerie te gebruik

Pasiënte moet ingelig word dat hulle nie moet bestuur of masjinerie te gereedskap hanteer indien hulle disseligheid of verswakte sig het. (sien **NEWE EFFEKTE**).

Laktose

LINOBACT FC tablette bevat laktose. Pasiënte met die selkame oorfleete bestande van galaktose intoleransie of galaktosemie. Lep laktase lakort of waarskynlike van laktose-galaktose behoort nie LINOBACT FC te gebruik nie. LINOBACT FC mag 'n effek hê op die glukemiese beheer by pasiënte met diabetes mellitus.

INTERAKSIES

LINOBACT FC word teenaangedui vir pasiënte wat behandel word met monoamienoksidase inhibeerders of binne twee weke van die inname van sulke medikasie (sien **KONTRAINDIKASIES**).

LINOBACT FC is 'n omkeerbare, nie-selektiewe monoamienoksidase-inhibeerder (MAOI). Dit veroorsaak 'n ligte, omkeerbare versterking van die pressor reaksie veroorsaak deur pseudo-epinefrin en fenielpropanolamien-hidrochloried. Potensieë interaksies met spesiale adrenerjiese middels moet oorweeg word (sien **WAARSKUWINGS EN SPESIALE VOORSORGMATREELS**). Dosisse van verbindings soos opium of pinerinen (adrenalin), behoort getreer te word om die gewenste respons te kry.

Cytochroom P450 interaksies

LINOBACT FC word nie opspoorbaar deur die sitochroom P450 (CYP) ensiemsisteam gemetaboliseer nie, en geen induksie of inhibisie van die aktiwiteit van klinies beduidende vorms van die menslike CYP isoënsieme (1A2, 2C9, 2C19, 2D6, 2E1, 3A4) vind plaas nie. Geen CYP450-geïnduseerde geneesmiddelretorsies word dus verwag nie. Fenitoin, wat as CYP2C9-substraat optree, mag saam met LINOBACT FC toegedien word sonder om die doseringsregimeel te verander.

Geen interaksies is met asteroom of gentamisien waargeneem nie.

Tiramiënrjke voedsel

Oormatige hoeveelhede voedsel of drankte met 'n hoë tiramien inhoud (bv. ryj kaas, gisektrakte, alkoholiese drankte nie gedistilleer is nie, en gefermende sojaboon produkte soos sojasous) behoort vermy te word om 'n pressor respons te voorkom.

Serotonergiese interaksies

Serotoniensindroom, geassosier met die gelykmatige toediening van linesolied en serotonerjiese middels, insluitend antidepressante soos selektiewe serotonienheropname-inhibeerders (SSRIs) is aangemeld (sien **KONTRAINDIKASIES** en **WAARSKUWINGS EN SPESIALE VOORSORGMATREELS**).

Alhoewel LINOBACT FC die potensiaal besit vir interaksie met serotonerjiese middels, is geen serotonerjiese uitwerkingss waargeneem in pasiënte wat linesolied en deksametorfonaan ontvang het nie.

Opioïede pynstillers

Petiëne behoort nie aan pasiënte toegedien te word wat MAO-inhibeerders (insluitend LINOBACT FC) neem, of binne 14 dae van die staking daarvan nie. Baie erge reaksies, insluitende koma, erge respiratoriese depressie, sianose en hipotensie mag voorkom.

Rifampisien

Die gelyktydige toediening van rifampisien saam met LINOBACT FC mag 'n verlindiging van ongeveer 20 % in linesolied K_{max} en 'n vermindering van ongeveer 30 % in linesolied AUC veroorsaak. Die meganisme van hierdie interaksie en die kliniese betekenis daarvan is onbekend.

MENSLIKE VOORTPLANTING

Swangerskap en laktasie

Die gebruik van LINOBACT FC-tablette in swangerskap en laktasie is teenaangedui, want veiligheid is nie gedomonstreer nie.

LINOBACT FC mag in borsmelk afgeskei word.

Fertiliteit

Linosolied, soos in LINOBACT FC, het vrugbaarheid omkeerbaar verlaag en geïnduseerde abnormale sperm morfologie in diere veroorsaak. Die moontlike effek op die menslike manlike voortplantingsstelsel is nie vasgestel nie.

DOSEERING EN GEBRUIKSAAFWYSINGS

LINOBACT FC tablette mag as aanvangstherapie gebruik word. Wanneer klinies aangewysde maë paënte wat behandeling op die parenterale formule aanpassing, oorgeskakel word na die tablet formule. In sulke omstandighede word geen dosisaanpassing benodig nie, aangesien LINOBACT FC in orale bioeskikbaarheid van ongeveer 100 % besit. LINOBACT FC tablette mag met of sonder voedsel geneem word. Die aanbevole doseringskedule vir LINOBACT FC is as volg:

Volwasse en Adoloesente (12 jaar en ouer) pasiënte:

Infeksies (insluitend dié wat met gelyktydige bakteriemie geassosieer word)	Dosering en roete van toediening	Duur van behandeling
Gemeenskapverworwe pneumonie, insluitend gelyktydige bakteriemie	600 mg oraal elke 12 uur	10 – 14 dae
Nosokomiale pneumonie, insluitend gelyktydige bakteriemie.	600 mg oraal elke 12 uur, soos bepaal deur kliniese erns	10 – 14 dae
Vel- en sagte weefselinfeksies, insluitend gelyktydige bakteriemie	600 mg oraal elke 12 uur, soos bepaal deur kliniese erns	10 – 14 dae
Enterokokkale infeksies, insluitend vankomisien-weerstandige infeksies, en dié met gelyktydige bakteriemie	600 mg oral elke 12 uur	14 – 28 opeenvolgende dae

By pasiënte jonger as 12 jaar, is die aanbevole dosis 10 mg/kg elke 8 uur. Hierdie dosis is nie gepas vir gebruik in kinders nie, aangesien LINOBACT FC nie verkrag kan word nie; vermy asseblief na die dosering aanbevelings in professionele inligting of die orale suspensie formules van linesolied.

Bejaarde pasiënte:

Geen dosisaanpassing is nodig nie.

Pasiënte met renale ontoereikendheid:

- Pasiënte met ligte tot matige renale ontoereikendheid, m.a.w. CL_{cr} (kreatinienruiming) < 30 ml/min.

Geen dosisaanpassing is nodig nie.

- Pasiënte met ernstige renale ontoereindheid (d.i. CL_{cr} < 30 ml/min.): Dosis behoort nie verander te word in hierdie pasiënte nie. Bewyse teen egerste dat kindereërmate vermindering van LINOBACT FC ophou in pasiënte met ernstige nier ontoereikendheid. Die kliniese betekenis is nie vasgestel nie. LINOBACT FC behoort met spesiale versigtigheid by hierdie pasiënte gebruik te word en slegs wanneer daar gedink word dat die verwagte voordeel die toetreesie risiko sal oorskry.

Hemodialise:

LINOBACT FC behoort na dialise by pasiënte wat sulke behandeling ontvang, gegee te word.

Pasiënte met hepatisse ontoereikendheid:

Geen dosisaanpassing is nodig nie.

NEWE EFFEKTE

Infeksies en infestasies:

Dikwels: Orale en vaginale monoliasis, moniliasie of swaminfeksie.

Minder dikwels: Antibiotika geassosieerde kalties, *Clostridium difficile* geassosieerde diarree (CDD), pseudomonasbræuse kolitis (of kalit, sien **WAARSKUWINGS EN SPESIALE VOORSORGMATREELS**), vaginitis.

Bloed en limfatiese sisteemversteurings:

Minder dikwels: Myelosuppressie* met anemie*, eosinofilie, leukopenie*, neutropenie, trombotisopenie*, pansitopenie*, sideroblastiese anemie*.

Immunitetstel versteurings:

Frekwensies onbekend: Hipersensitiewe reaksies, anafilaakse, angio-edeem, bulus velfafklyngs soos Stevens-Johnson-sindroom en toksiese epidemale nekrolise.

Metaboliese en voedingsversteurings:

Minder dikwels: Verhoogde serumkreatinienfosfokinase, hiperglisemie, laktiese asidose*, hiponatremie.

Psigiatriese versteurings:

Dikwels: Slaaptoesheid.

Senuweestelsel versteurings:

Dikwels: Hoofpyn; smaakverandering, metaalagtige smaak.

Minder dikwels: Duisagtigheid, hiposteësie, parestesie, perifere neuropatie*, konvulsies*, serotoniensindroom.**

Oogafklyngs:

Minder dikwels: Versteurde visie*, optiese neuropatie*, optiese neuritis*, verlies van visie*, veranderinge in gesigskerpte*, veranderinge in kleurvisie*, veranderinge in gesigsvelddefek.*

Oor- en labintafklyngs:

Minder dikwels: Tinnitus.

Harafklyngs:

Minder dikwels: Disritmie (tachycardia).

Vaskulêre versteurings: