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

A 20.1.1 Broad and 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 sensitivity.

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^{-9} to 1×10^{-11}.

Cross-resistance between linezolid and the following medicines 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 isoforms (1A2, 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); the clinical significance has not yet been established. As

approximately 30 % of a 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 of 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 **DOSAGE 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 pneumonia*e (including multi-drug resistant

S. pneumoniae (MDRSP)[1] 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)[1] 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*.

[1]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 oxidases 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

Superinfection: Treatment with LINOBACT FC alters the normal flora of the colon, which may lead to excessive growth of non-susceptible organisms such as Candida and *Clostridium difficile*.

Antibiotic-associated diarrhoea (AAD), *Clostridium difficile* – associated diarrhoea (CDAD) and pseudomembranous colitis has been reported with linezolid (contained in LINOBACT FC) and may vary in seriousness from mild diarrhoea to fatal colitis. It is therefore important to consider this diagnosis in patients presenting with diarrhoea after administration of LINOBACT FC.

Should superinfection occur during therapy, appropriate treatment should be instituted. The risk/benefit should be thoroughly considered in patients with worsening diarrhoea.

Lactic acidosis

Lactic acidosis has been reported with the use of LINOBACT FC. Immediate medical attention is required in patients who develop signs and symptoms of metabolic acidosis, including recurrent nausea or vomiting, abdominal pain, a low bicarbonate level, or hyperventilation while receiving LINOBACT FC. If lactic acidosis occurs, the benefits of continued use of LINOBACT FC should be weighed against the potential risks.

Mitochondrial dysfunction

Linezolid, contained in LINOBACT FC, 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 LINOBACT FC is used longer than 28 days.

Myelosuppression

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 serotonin 5-HT_1 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, phaeochromocytoma, carcinoid syndrome, untreated hyperthyroidism, bipolar depression, schizoaffective 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 porphyrinogenic 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 enhancement of the pressor responses induced by pseudoephedrine and phenylpropanolamine 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 isoforms (1A2, 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 serotonin 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.

DOSAGE 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		
Skin and soft tissue infections, including concurrent bacteraemia	600 mg orally every 12 hours, depending on clinical severity	
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 (d.i. 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 monoliasis, 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 discolouration 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 discolouration.

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 overdosage, supportive care is advised together with maintenance of glomerular filtration. Approximately 30 % of a 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 30 °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

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