



ספטמבר 2016

פיזר פי אף אי פרמצבטיקה ישראל בע"מ
רח' שנקר 9, ת.ד. 12133
הרצליה פיתוח, ישראל 46725
טל: 972-9-9700500 פקס: 972-9-9700501
פיזר פי אף אי פרמצבטיקה ישראל בע"מ

רופא/ה, רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלונים לרופא ולצרכן של **Zyvoxid IV 2 mg/ml + Zyvoxid 600 mg TAB** :
קו תחתי משמעו תוספת טקסט, קו חוצה משמעו מחיקת טקסט, הדגשה משמעה החמרה.

Linezolid 600 mg

Indicated for:

Therapy is indicated only when an organism resistant to all other antibiotics is suspected.

Zyvoxid is indicated in adult and pediatric patients for the treatment of infections when known or suspected to be caused by susceptible organisms including those associated with concurrent bacteraemia such as:

- 1) Pneumonia - community acquired and nosocomial pneumonia including multi drug resistant streptococcus pneumonia (MDRSP).
- 2) Skin and soft tissue infections including diabetic foot infections.
- 3) Enterococcal infections.

Combination therapy may be indicated if a concomitant Gram negative pathogen is documented or suspected.

להלן העדכונים העיקריים בעלון לרופא:

4.1 Therapeutic indications

...

Linezolid should only be initiated after consultation with a relevant specialist such as a microbiologist or infectious diseases specialist.

4.3. Contraindications

Hypersensitivity to linezolid or to any of the excipients in the relevant pharmaceutical form (see section 6.1).

Monoamine Oxidase Inhibitors

Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within two weeks of taking any such medicinal product.

Potential Interactions Producing Elevation of Blood Pressure

Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine, phenylpropanolamine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine) (see section 4.5).

Potential Serotonergic Interactions

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT₁ receptor agonists (triptans), meperidine or buspirone (see section 4.5)

Hypersensitivity to linezolid or to any of the excipients listed in section 6.1.

Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid, **selegiline, moclobemide**) or within two weeks of taking any such medicinal product.

Unless there are facilities available for close observation and monitoring of blood pressure, linezolid 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 (see section 4.4), tricyclic antidepressants, serotonin 5-HT₁ receptor agonists (triptans), directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration (see section 4.6).

4.4. Special warnings and precautions for use

Pseudomembranous colitis has been reported with nearly all antibacterial agents including linezolid, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including linezolid, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD.

Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile* and surgical evaluation should be instituted as clinically indicated.

The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.

The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established.

Zyvoxid has not been studied in patients with uncontrolled hypertension, pheochromocytoma carcinoid syndrome, or untreated hyperthyroidism.

Peripheral neuropathy and optic neuropathy have been reported in patients treated with linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration.

If symptoms of visual impairment appear, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. Visual function should be monitored in all patients taking linezolid for extended periods (greater than or equal to 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with linezolid. If peripheral or optic neuropathy occurs, the continued use of linezolid in these patients should be weighed against the potential risks.

Lactic acidosis has been reported with the use of linezolid. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical attention.

Convulsions have been reported to occur rarely in patients when treated with linezolid.

In most of these cases, a history of seizures or risk factors for seizures was reported. 51 spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Where administration of Zyvoxid and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination.

If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed. In healthy volunteers, coadministration of rifampin with linezolid resulted in a 21% decrease in linezolid C_{max} and a 32% decrease in linezolid AUC (see section 4.5). The clinical significance of this interaction is unknown.

Linezolid has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected.

Linezolid should be used with special caution in patients at high risk for life threatening systemic infections, such as those with infections related to central venous catheters in intensive care units.

Linezolid is not approved for the treatment of patients with catheter-related bloodstream infections.

Clinical Trial in Catheter-Related Gram-Positive Bloodstream Infections

An open-label, randomized clinical trial was conducted in adult patients with catheter-related Gram-positive bloodstream infections comparing linezolid (600 mg q12h IV/PO) to vancomycin 1 g IV q12h or oxacillin 2 g IV q6h/dicloxacillin 500 mg PO q6h with a treatment duration of 7 to 28 days. The mortality rates in this study were 78/363 (21.5%) and 58/363 (16.0%) on linezolid and the comparator, respectively. Based on results from a logistic regression, the estimated odds ratio is 1.426 [95% CI 0.970, 2.098]. While causality has not been established, this observed imbalance occurred primarily in linezolid treated patients in whom either Gram-negative pathogens, mixed Gram-negative and Gram-positive pathogens, or no pathogen were identified at baseline. Patients randomized to linezolid who had only a Gram-positive including the subgroup of patients with Gram-positive bacteremia experienced a survival rate similar to the comparator.

Myelosuppression

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pretreatment levels. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with linezolid may be at greater risk of experiencing blood dyscrasias than younger patients.

Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis. Therefore, close monitoring of blood counts is recommended in patients who: have pre-existing anaemia, granulocytopenia or thrombocytopenia; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; receive more than 10-14 days of therapy. Linezolid should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible.

If significant myelosuppression occurs during linezolid therapy, treatment should be stopped unless it is considered absolutely necessary to continue therapy, in which case intensive monitoring of blood counts and appropriate management strategies should be implemented.

In addition, it is recommended that complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) should be monitored weekly in patients who receive linezolid regardless of baseline blood count.

In compassionate use studies, a higher incidence of serious anaemia was reported in patients receiving linezolid for more than the maximum recommended duration of 28 days. These patients more often required blood transfusion. Cases of anaemia requiring blood transfusion have also been reported post marketing, with more cases occurring in patients who received linezolid therapy for more than 28 days.

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.

Mortality imbalance in a clinical trial in patients with catheter-related Gram positive bloodstream infections

Excess mortality was seen in patients treated with linezolid, relative to vancomycin/dicloxacillin/oxacillin, in an open-label study in seriously ill patients with intravascular catheter-related infections [78/363 (21.5%) vs 58/363 (16.0%)]. The main factor influencing the

mortality rate was the Gram positive infection status at baseline. Mortality rates were similar in patients with infections caused purely by Gram positive organisms (odds ratio 0.96; 95% confidence interval: 0.58-1.59) but were significantly higher ($p=0.0162$) in the linezolid arm in patients with any other pathogen or no pathogen at baseline (odds ratio 2.48; 95% confidence interval: 1.38-4.46). The greatest imbalance occurred during treatment and within 7 days following discontinuation of study drug. More patients in the linezolid arm acquired Gram negative pathogens during the study and died from infection caused by Gram negative pathogens and polymicrobial infections. Therefore, in complicated skin and soft tissue infections linezolid should only be used in patients with known or possible co-infection with Gram negative organisms if there are no alternative treatment options available (see section 4.1). In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

Antibiotic-associated diarrhoea and colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent. In cases of suspected or verified antibiotic-associated colitis, discontinuation of linezolid may be warranted. Appropriate management measures should be instituted.

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of nearly all antibiotics including linezolid and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of linezolid. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including linezolid, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

Lactic acidosis

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

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 the drug is used longer than 28 days.

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid 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 section 4.3) except where administration of linezolid and concomitant serotonergic agents is essential. In those cases patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuing either one or both agents; if the concomitant serotonergic agent is withdrawn, discontinuation symptoms can occur.

Peripheral and optic neuropathy

Peripheral neuropathy, as well as optic neuropathy and optic neuritis sometimes progressing to loss of vision, have been reported in patients treated with Linezolid; these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days.

All 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. If any patients are

taking Linezolid for longer than the recommended 28 days, their visual function should be regularly monitored.

If peripheral or optic neuropathy occurs, the continued use of Linezolid should be weighed against the potential risks.

There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medications for the treatment of tuberculosis.

Convulsions

Convulsions have been reported to occur in patients when treated with Linezolid. In most of these cases, a history of seizures or risk factors for seizures was reported. Patients should be advised to inform their physician if they have a history of seizures.

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI); however, at the doses used for antibacterial therapy, it does not exert an anti-depressive effect. There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (see sections 4.3 and 4.5).

Use with tyramine-rich foods

Patients should be advised against consuming large amounts of tyramine rich foods (see section 4.5).

Superinfection

The effects of linezolid therapy on normal flora have not been evaluated in clinical trials.

The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. For example, approximately 3% of patients receiving the recommended linezolid doses experienced drug-related candidiasis during clinical trials. Should superinfection occur during therapy, appropriate measures should be taken.

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 (see sections 4.2 and 5.2).

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk (see sections 4.2 and 5.2).

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 (see section 5.3).

Clinical trials

The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established.

Controlled clinical trials did not include patients with diabetic foot lesions, decubitus or ischaemic lesions, severe burns or gangrene. Therefore, experience in the use of linezolid in the treatment of these conditions is limited.

Excipients

Each ml of the solution contains 45.7 mg (i.e. 13.7 g/300 ml) glucose. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance. Each ml of solution also contains 0.38 mg (114 mg/300 ml) sodium. The sodium content should be taken into account in patients on a controlled sodium diet.

...

4.5. Interaction with other medicinal products and other forms of interaction

Linezolid is not detectably metabolized 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 drug interactions are expected with linezolid. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Linezolid is a weak, reversible, non-selective monoamine oxidase inhibitor (MAOI).

Clinical studies have shown that it produces a mild, reversible enhancement of the pressor responses induced by pseudoephedrine and phenylpropanolamine hydrochloride. Thus, the potential for interaction with sympathomimetic or adrenergic agents should be considered and doses of compounds, such as dopamine or epinephrine, should be titrated to achieve the desired response.

No significant pressor response was observed in subjects receiving both linezolid and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting excessive amounts of food and beverages with a high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverage, fermented soya bean products such as soy sauce). In subjects receiving linezolid and tyramine doses of more than 100 mg, a significant pressor response has been observed.

Although linezolid has the potential for interaction with serotonergic agents, no serotonin syndrome effects (e.g. confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) were observed in subjects receiving linezolid and dextromethorphan.

Since there is limited experience with concomitant administration of linezolid and serotonergic agents, physicians should be alert to the possibility of signs and symptoms of serotonin syndrome (e.g., hyperpyrexia and cognitive dysfunction) in patients receiving such concomitant therapy.

Very rare spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic agents have been reported.

Antibiotics: The pharmacokinetics of linezolid were not altered when administered together with either aztreonam or gentamicin. The effect of rifampin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampin 600 mg once daily for 8 days. Rifampin decreased the linezolid C_{max} and AUC by a mean 21% [90% CI, 15, 27] and a mean 32% [90% CI, 27, 37], respectively. The mechanism of this interaction and its clinical significance are unknown (see section 4.4).

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI). There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients on concomitant medications that might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (see sections 4.3 and 4.4).

Potential interactions producing elevation of blood pressure

In normotensive healthy volunteers, linezolid enhanced the increases in blood pressure caused by pseudoephedrine and phenylpropanolamine hydrochloride. Co-administration of linezolid with either pseudoephedrine or phenylpropanolamine resulted in mean increases in systolic blood pressure of the order of 30-40 mmHg, compared with 11-15 mmHg increases with linezolid alone, 14-18 mmHg with either pseudoephedrine or phenylpropanolamine alone and 8-11 mmHg with placebo. Similar studies in hypertensive subjects have not been conducted. It is recommended that doses of drugs with a vasopressive action, including dopaminergic agents, should be carefully titrated to achieve the desired response when co-administered with linezolid.

Potential serotonergic interactions

The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20 mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

Post marketing experience: there has been one report of a patient experiencing serotonin syndrome-like effects while taking linezolid and dextromethorphan which resolved on discontinuation of both medications.

During clinical use of linezolid with serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), cases of serotonin syndrome have been reported. Therefore, while co-administration is contraindicated (see section 4.3), management of patients for whom treatment with linezolid and serotonergic agents is essential, is described in section 4.4.

Use with tyramine-rich foods

No significant pressor response was observed in subjects receiving both linezolid and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting excessive amounts of food and beverages with a high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

Drugs metabolised by cytochrome P450

Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450-induced drug interactions are expected with linezolid.

Rifampicin

The effect of rifampicin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased the linezolid C_{max} and AUC by a mean 21% [90% CI, 15, 27] and a mean 32% [90% CI, 27, 37], respectively. The mechanism of this interaction and its clinical significance are unknown.

Warfarin

When warfarin was added to linezolid therapy at steady-state, there was a 10% reduction in mean maximum INR on co-administration with a 5% reduction in AUC INR. There are insufficient data from patients who have received warfarin and linezolid to assess the clinical significance, if any, of these findings.

4.6. Fertility, pregnancy and lactation

...

Fertility

In animal studies, linezolid caused a reduction in fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

Patients should be warned about the potential for dizziness or symptoms of visual impairment (as described in section 4.4 and 4.8) whilst receiving linezolid and should be advised not to drive or operate machinery if any of these symptoms occurs.

4.8 Undesirable effects

Clinical Trials:

Adverse events considered drug related in controlled clinical trials with an incidence of at least 1% were:

Gastrointestinal Disorders: Abdominal pain/cramps/distension, diarrhea, nausea, vomiting.

Infections and Infestations: Moniliasis.

Investigations: Abnormal hematology tests, abnormal liver function tests.

Nervous System Disorders: Headache, taste alteration.

Post marketing:

Blood and Lymphatic System Disorders: Reversible anemia, leucopenia, thrombocytopenia, pancytopenia.

Eye Disorders: Optic neuropathy sometimes progressing to loss of vision, have been reported in patients

treated with linezolid. These reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days (see section 4.4).

Immune System Disorders: Anaphylaxis.

Metabolism and Nutrition Disorders: Lactic acidosis (see section 4.4).

Nervous System Disorders: Peripheral neuropathy, convulsions (see section 4.4).

Skin and Subcutaneous Tissue Disorders: Rash, angioedema. Very rare reports of bullous skin disorders such as those described as Stevens Johnson syndrome have been received.

Gastrointestinal Disorders: Tongue discoloration. Superficial tooth discoloration has been reported very rarely with the use of linezolid. The discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome.

Pediatric Patients:

The safety of Zyvoxid formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with Zyvoxid were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid: vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. Table 2 shows the incidence of adverse events reported in at least 2% of pediatric patients treated with Zyvoxid in these trials.

Table 2. Incidence (%) of Adverse Events Reported in ≥2% of Pediatric Patients Treated with Zyvoxid in Comparator-Controlled Clinical Trials

Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
	Zyvoxid (n=248)	Cefadroxil (n = 251)	Zyvoxid (n = 215)	Vancomycin (n=101)
Fever	2.9	3.6	14.1	14.1
Diarrhea	7.8	8.0	10.8	12.1
Vomiting	2.9	6.4	9.4	9.4
Sepsis	0	0	8.0	7.1
Rash	1.6	1.2	7.0	15.2
Headache	6.5	4.0	0.9	0
Anemia	0	0	5.6	7.1
Thrombocytopenia	0	0	4.7	2.0
Upper respiratory infection	3.7	5.2	4.2	1.0
Nausea	3.7	3.2	1.9	0
Dyspnea	0	0	3.3	1.0
Reaction at site of injection or of vascular catheter	0	0	3.3	5.1
Trauma	3.3	4.8	2.8	2.0
Pharyngitis	2.9	1.6	0.5	1.0
Convulsion	0	0	2.8	2.0
Hypokalemia	0	0	2.8	3.0
Pneumonia	0	0	2.8	2.0
Thrombocythemia	0	0	2.8	2.0
Cough	2.4	4.0	0.9	0
Generalized abdominal pain	2.4	2.8	0.9	2.0
Localized abdominal pain	2.4	2.8	0.5	1.0
Apnea	0	0	2.3	2.0
Gastrointestinal bleeding	0	0	2.3	1.0
Generalized edema	0	0	2.3	1.0

Loose stools	1.6	0.8	2.3	3.0
Localized pain	2.0	1.6	0.9	0
Skin disorder	2.0	0	0.9	1.0
* Patients 5 through 11 years of age received Zyvoxid 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received Zyvoxid 600 mg PO q12h or cefadroxil 500 mg PO q12h.				
† Patients from birth through 11 years of age received Zyvoxid 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.				

Table 3 shows the incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

Table 3. Incidence (%) of Drug-related Adverse Events Occurring in >1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-Controlled Clinical Trials				
Event	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
	Zyvoxid (n=248)	Cefadroxil (n=251)	Zyvoxid (n=215)	Vancomycin (n=101)
% of patients with ≥1 drug-related adverse event	19.2	14.1	18.8	34.3
% of patients discontinuing due to a drug-related adverse event	1.6	2.4	0.9	6.1
Diarrhea	5.7	5.2	3.8	6.1
Nausea	3.3	2.0	1.4	0
Headache	2.4	0.8	0	0
Loose stools	1.2	0.8	1.9	0
Thrombocytopenia	0	0	1.9	0
Vomiting	1.2	2.4	1.9	1.0
Generalized abdominal pain	1.6	1.2	0	0
Localized abdominal pain	1.6	1.2	0	0
Anemia	0	0	1.4	1.0
Eosinophilia	0.4	0.4	1.4	0
Rash	0.4	1.2	1.4	7.1
Vertigo	1.2	0.4	0	0
Oral moniliasis	0	0	0.9	4.0
Fever	0	0	0.5	3.0
Pruritus at non-application site	0.4	0	0	2.0
Anaphylaxis	0	0	0	10.1‡
* Patients 5 through 11 years of age received Zyvoxid 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received Zyvoxid 600 mg PO q12h or cefadroxil 500 mg PO q12h.				
† Patients from birth through 11 years of age received Zyvoxid 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.				
‡ These reports were of 'red-man syndrome', which were coded as anaphylaxis.				

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 2,000 adult patients who received the recommended linezolid doses for up to 28 days.

Those most commonly reported were diarrhoea (8.4%), headache (6.5%), nausea (6.3%) and vomiting (4.0%).

The most commonly reported drug-related adverse events which led to discontinuation of treatment were headache, diarrhoea, nausea and vomiting. About 3% of patients discontinued treatment because they experienced a drug-related adverse event.

Additional adverse reactions reported from post-marketing experience are included in the table with frequency category 'Not known', since the actual frequency cannot be estimated from the available data.

The following undesirable effects have been observed and reported during treatment with linezolid with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); Not known (cannot be estimated from the available data)

<u>System Organ Class</u>	<u>Common</u> <u>($\geq 1/100$ to $< 1/10$)</u>	<u>Uncommon</u> <u>($\geq 1/1,000$ to $< 1/100$)</u>	<u>Rare</u> <u>($\geq 1/10,000$ to $< 1/1,000$)</u>	<u>Very Rare</u> <u>($< 1/10,000$)</u>	<u>Frequency not known (cannot be estimated from available data)</u>
<u>Infections and infestations</u>	candidiasis, oral candidiasis, vaginal candidiasis, fungal infections	vaginitis	antibiotic-associated colitis, including pseudomembranous colitis*		
<u>Blood and the lymphatic system disorders</u>	anaemia*†	leucopenia*, neutropenia, thrombocytopenia*, eosinophilia	pancytopenia*		myelosuppression*, sideroblastic anaemia*
<u>Immune system disorders</u>					anaphylaxis
<u>Metabolism and nutrition disorders</u>		hyponatraemia			lactic acidosis*
<u>Psychiatric disorders</u>	insomnia				
<u>Nervous system disorders</u>	headache, taste perversion (metallic taste), dizziness	convulsions*, hypoesthesia, paraesthesia			serotonin syndrome**, peripheral neuropathy*
<u>Eye disorders</u>		blurred vision*	changes in visual field defect*		optic neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*
<u>Ear and labyrinth disorders</u>		tinnitus			
<u>Cardiac disorders</u>		arrhythmia (tachycardia)			
<u>Vascular disorders</u>	hypertension	transient ischaemic attacks, phlebitis, thrombophlebitis			
<u>Gastrointestinal disorders</u>	diarrhoea, nausea, vomiting, localised or general abdominal pain, constipation, dyspepsia	pancreatitis, gastritis, abdominal distention, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder	superficial tooth discolouration		
<u>Hepato-biliary disorders</u>	abnormal liver function test; increased AST, ALT or alkaline	increased total bilirubin			

<u>System Organ Class</u>	<u>Common</u> (≥1/100 to <1/10)	<u>Uncommon</u> (≥1/1,000 to <1/100)	<u>Rare</u> (≥1/10,000 to <1/1,000)	<u>Very Rare</u> (≤1/10,000)	<u>Frequency not known (cannot be estimated from available data)</u>
	<u>phosphatase</u>				
<u>Skin and subcutaneous tissue disorders</u>	<u>pruritus, rash</u>	<u>urticaria, dermatitis, diaphoresis</u>			<u>bullous disorders such as those described as Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, alopecia</u>
<u>Renal and urinary disorders</u>	<u>increased BUN</u>	<u>renal failure, increased creatinine, polyuria</u>			
<u>Reproductive system and breast disorders</u>		<u>vulvovaginal disorder</u>			
<u>General disorders and administration site conditions</u>	<u>fever, localised pain</u>	<u>chills, fatigue, injection site pain, increased thirst</u>			
<u>Investigations</u>	<u>Chemistry</u> <u>Increased LDH, creatine kinase, lipase, amylase or non fasting glucose.</u> <u>Decreased total protein, albumin, sodium or calcium.</u> <u>Increased or decreased potassium or bicarbonate.</u> <u>Haematology</u> <u>Increased neutrophils or eosinophils.</u> <u>Decreased haemoglobin, haematocrit or red blood cell count.</u> <u>Increased or decreased platelet or white blood cell counts.</u>	<u>Chemistry</u> <u>Increased sodium or calcium. Decreased non fasting glucose.</u> <u>Increased or decreased chloride.</u> <u>Haematology</u> <u>Increased reticulocyte count.</u> <u>Decreased neutrophils.</u>			

* See section 4.4.

** See sections 4.3 and 4.5

† See below

The following adverse reactions to linezolid were considered to be serious in rare cases: localised abdominal pain, transient ischaemic attacks and hypertension.

†In controlled clinical trials where linezolid was administered for up to 28 days, 2.0% of the patients reported anaemia. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for >28 days. The proportion of cases reporting drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for >28 days.

Paediatric population

The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid: vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established.

Of the pediatric patients treated for uSSSIs, 19.2% of ZYVOX-treated and 14.1% of comparator-treated patients experienced at least one drug-related adverse event. For all other indications, 18.8% of ZYVOX-treated and 34.3% of comparator-treated patients experienced at least one drug-related adverse event.

Table 3 shows the incidence of all-causality, treatment-emergent adverse reactions reported in more than 1% of pediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

Table 3. Incidence (%) of Treatment-Emergent Adverse Reactions Occurring in > 1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-Controlled Clinical Trials

<u>ADVERSE REACTIONS</u>	<u>Uncomplicated Skin and Skin Structure Infections*</u>		<u>All Other Indications†</u>	
	<u>ZYVOX (n=248)</u>	<u>Cefadroxil (n=251)</u>	<u>ZYVOX (n=215)</u>	<u>Vancomycin (n=101)</u>
<u>Diarrhea</u>	<u>7.8</u>	<u>8.0</u>	<u>10.8</u>	<u>12.1</u>
<u>Vomiting</u>	<u>2.9</u>	<u>6.4</u>	<u>9.4</u>	<u>9.1</u>
<u>Headache</u>	<u>6.5</u>	<u>4.0</u>	<u>0.9</u>	<u>0</u>
<u>Anemia</u>	<u>0</u>	<u>0</u>	<u>5.6</u>	<u>7.1</u>
<u>Thrombocytopenia</u>	<u>0</u>	<u>0</u>	<u>4.7</u>	<u>2.0</u>
<u>Nausea</u>	<u>3.7</u>	<u>3.2</u>	<u>1.9</u>	<u>0</u>
<u>Generalized abdominal pain</u>	<u>2.4</u>	<u>2.8</u>	<u>0.9</u>	<u>2.0</u>
<u>Localized abdominal pain</u>	<u>2.4</u>	<u>2.8</u>	<u>0.5</u>	<u>1.0</u>
<u>Loose stools</u>	<u>1.6</u>	<u>0.8</u>	<u>2.3</u>	<u>3.0</u>
<u>Eosinophilia</u>	<u>0.4</u>	<u>0.8</u>	<u>1.9</u>	<u>1.0</u>
<u>Pruritus at non-application site</u>	<u>0.8</u>	<u>0.4</u>	<u>1.4</u>	<u>2.0</u>
<u>Vertigo</u>	<u>1.2</u>	<u>0.4</u>	<u>0</u>	<u>0</u>

*** Patients 5 through 11 years of age received ZYVOX 10 mg/kg by mouth every 12 hours or cefadroxil 15 mg/kg by mouth every 12 hours. Patients 12 years or older received ZYVOX 600 mg by mouth every 12 hours or cefadroxil 500 mg by mouth every 12 hours.**

† Patients from birth through 11 years of age received ZYVOX 10 mg/kg intravenously by mouth every 8 hours or vancomycin 10 to 15 mg/kg intravenously every 6-24 hours, depending on age and renal clearance.

Of the pediatric patients treated for uSSSIs, 1.6% of ZYVOX-treated and 2.4% of comparator-treated patients discontinued treatment due to drug-related adverse events. For all other indications, discontinuations due to drug-related adverse events occurred in 0.9% of ZYVOX-treated and 6.1% of comparator-treated patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>).

5.1 Pharmacodynamic properties

General Properties

Linezolid is a synthetic, antibacterial agent that belongs to a new class of antimicrobials, the oxazolidinones. It has in vitro activity against aerobic Gram positive bacteria, some Gram negative bacteria and anaerobic microorganisms. Linezolid selectively inhibits bacterial protein synthesis via a unique mechanism of action. Specifically, it binds to a site on the bacterial ribosome (23S of the 50S subunit) and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process.

Susceptibility

Only microorganisms relevant to the given clinical indications are presented here.

Susceptible organisms

Gram-positive aerobes:

Enterococcus faecalis

*Enterococcus faecium**

*Staphylococcus aureus**

Coagulase negative staphylococci

*Streptococcus agalactiae**

*Streptococcus pneumoniae**

*Streptococcus pyogenes**

Group C streptococci

Group G streptococci

Gram-positive anaerobes:

Clostridium perfringens

Peptostreptococcus anaerobius

Peptostreptococcus species

Resistant organisms

Haemophilus influenzae

Moraxella catarrhalis

Neisseria species

Enterobacteriaceae

Pseudomonas species

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

Pharmacotherapeutic group: Other antibacterials, ATC code: J 01 X X 08

General Properties

Linezolid is a synthetic, antibacterial agent that belongs to a new class of antimicrobials, the oxazolidinones. It has in vitro activity against aerobic Gram positive bacteria and anaerobic micro-organisms. Linezolid selectively inhibits bacterial protein synthesis via a unique mechanism of action. Specifically, it binds to a site on the bacterial ribosome (23S of the 50S subunit) and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process.

The in vitro postantibiotic effect (PAE) of linezolid for *Staphylococcus aureus* was approximately 2 hours. When measured in animal models, the in vivo PAE was 3.6 and 3.9 hours for *Staphylococcus aureus* and *Streptococcus pneumoniae*, respectively. In animal studies, the key pharmacodynamic parameter for efficacy was the time for which the linezolid plasma level exceeded the minimum inhibitory concentration (MIC) for the infecting organism.

Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and enterococci are Susceptible \leq 4mg/L and Resistant >4 mg/L. For streptococci (including *S. pneumoniae*) the breakpoints are Susceptible \leq 2 mg/L and Resistant >4 mg/L.

Non-species related MIC breakpoints are Susceptible \leq 2 mg/L and Resistant > 4 mg/L. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that have not been given a specific breakpoint and not for those species where susceptibility testing is not recommended.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

<u>Category</u>
<u>Susceptible organisms</u> <u>Gram positive aerobes:</u> <u><i>Enterococcus faecalis</i></u> <u><i>Enterococcus faecium</i>*</u> <u><i>Staphylococcus aureus</i>*</u> <u>Coagulase negative staphylococci</u> <u><i>Streptococcus agalactiae</i>*</u> <u><i>Streptococcus pneumoniae</i>*</u> <u><i>Streptococcus pyogenes</i>*</u> <u>Group C streptococci</u> <u>Group G streptococci</u> <u>Gram positive anaerobes:</u> <u><i>Clostridium perfringens</i></u> <u><i>Peptostreptococcus anaerobius</i></u> <u><i>Peptostreptococcus</i> species</u>
<u>Resistant organisms</u> <u><i>Haemophilus influenzae</i></u> <u><i>Moraxella catarrhalis</i></u> <u><i>Neisseria</i> species</u> <u><i>Enterobacteriaceae</i></u> <u><i>Pseudomonas</i> species</u>

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

Whereas linezolid shows some in vitro activity against *Legionella*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, there are insufficient data to demonstrate clinical efficacy.

Resistance

Cross resistance

Linezolid's mechanism of action differs from those of other antibiotic classes. In vitro studies with clinical isolates (including methicillin-resistant staphylococci, vancomycin-resistant enterococci, and penicillin- and erythromycin-resistant streptococci) indicate that linezolid is usually active against organisms which are resistant to one or more other classes of antimicrobial agents.

Resistance to linezolid is associated with point mutations in the 23S rRNA.

As documented with other antibiotics when used in patients with difficult to treat infections and/or for prolonged periods, emergent decreases in susceptibility have been observed with linezolid. Resistance to linezolid has been reported in enterococci, Staphylococcus aureus and coagulase negative staphylococci. This generally has been associated with prolonged courses of therapy and the presence of prosthetic materials or undrained abscesses. When antibiotic-resistant organisms are encountered in the hospital it is important to emphasize infection control policies.

Information from clinical trials

Studies in the paediatric population:

In an open study, the efficacy of linezolid (10 mg/kg q8h) was compared to vancomycin (10-15mg/kg q6-24h) in treating infections due to suspected or proven resistant gram-positive pathogens (including nosocomial pneumonia, complicated skin and skin structure infections, catheter related bacteraemia, bacteraemia of unknown source, and other infections), in children from birth to 11 years. Clinical cure rates in the clinically evaluable population were 89.3% (134/150) and 84.5% (60/71) for linezolid and vancomycin, respectively (95%CI: -4.9, 14.6).

5.3 Preclinical safety data

...

Preclinical data, based on conventional studies of repeated-dose toxicity and genotoxicity, revealed no special hazard for humans beyond those addressed in other sections of this Summary of Product Characteristics. Carcinogenicity / oncogenicity studies have not been conducted in view of the short duration of dosing and lack of genotoxicity in the standard battery of studies.

...

6.3 Shelf life

Solution for infusion:

Before opening: 3 years.

After opening: From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Film coated tablets: 3 years.

6.3 Special Precautions for Storage

Solution for injection: Store below 25°C.

Solution for infusion: Keep bags in foil overwrap and carton until ready to use.

Tablets: Store below 25°C. Protect from light.

6.4 Special precautions for storage

Solution for infusion:

Store below 25°C.

Store in the original package (overwrap and carton) until ready to use in order to protect from light.

Film coated tablets:

Store below 25°C, protect from light.

6.5 Instructions for Use and Handling

Solution for infusion: Remove overwrap only when ready to use, then check for minute leaks by squeezing the bag firmly. If the bag leaks, do not use as sterility may be impaired. Do not use these bags in series connections. Any unused solution must be discarded.

Do not reconnect partially used bags.

Film-coated tablets: No special requirements.

6.6 Instructions for use and handling

Solution for infusion:

For single use only. Remove overwrap only when ready to use, then check for minute leaks by squeezing the bag firmly. If the bag leaks, do not use as sterility may be impaired. **The solution should be visually inspected prior to use and only clear solutions, without particles should be used.**

Do not use these bags in series connections. Any unused solution must be discarded. No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not reconnect partially used bags.

Linezolid solution for infusion is compatible with the following solutions: 5% glucose intravenous infusion, 0.9% sodium chloride intravenous infusion, Ringer-lactate solution for injection (Hartmann's solution for injection).

Film coated tablets:

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

להלן העדכונים העיקריים בעלון לצרכן:

...

מתי אין להשתמש בתרופה?

אין להשתמש אם ידועה רגישות לאחד ממרכיבי התרופה.
על־ל הפסיק להניק אם הינך צריכה לטול את התרופה.
אין לטול תרופה זו בו זמנית או תוך 14 יום לאחר מתן תרופות נגד דכאון מסוג בולמי-מונאמינאוקסידז (MAO).
אין להשתמש בתרופה זו שלא תחת מעקב אחר שינויים בלחץ דם בחולים עם לחץ דם גבוה שאינו מבוקר (כגון: חולים עם גידול בבלוטת יתרת הכליה מסוג פיאוכרומוטיצומה, רעלת בלוטת התריס), חולים הנוטלים תרופות המעלות לחץ דם (כגון: תרופות נגד הצטננות המכילות פסאודואפדרין, אפינפרין ודופמין).
אין להשתמש בתרופה זו שלא תחת מעקב אחר תסמינים של סינדרום סרטונין בו זמנית עם תרופות נגד דכאון, טריפטנים, מפרידין (mepredine), בוספירון ומעכבי סרטונין.

2. לפני השימוש בתרופה

אין להשתמש בתרופה אם:

- × אם אתה רגיש (אלרגי) לחומר הפעיל או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה.
- × הנך מניקה. מאחר והתרופה עוברת בחלב אם ועלולה לפגוע בתינוק.
- × אין לטול תרופה זו בו זמנית או תוך 14 יום לאחר מתן תרופות מסוג חוסמי מונאמינאוקסידז (MAOIs) (כגון: פנלזין, איזוקרבוקסאזיד, סלג'ילין, מוקלובמיד) הניתנות בדרך כלל לטיפול בדיכאון או במחלת פרקינסון.

אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול במקרים הבאים:

אם הינך בהריון.

אם הינך סובל/ת או סבלת בעבר מליקוי בתיפקוד מערכת העיכול (היסטוריה של שלשולים עקב טיפול באנטיביוטיקה) או מערכת הדם (בעיות במספר טסיות דם).

אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול:

- אם הנך סובל מלחץ דם גבוה.
- אם אובחנה אצלך פעילות יתר של בלוטת התריס (תירואיד).

- אם הנך סובל מגידול בבלוטות יותרת הכליה (אדרנל) או מתסמונת קרצינואידית (הנגרמת כתוצאה מגידולים במערכת ההורמונלית, התסמינים יכולים לכלול שלשולים, הסמקה בעור וקולות צפצוף בזמן הנשימה).
- אם הנך סובל ממאניה דיפרסיה, מהפרעה סכיזו-אפקטיבית, מבלבול פתולוגי ומבעיות נפשיות אחרות.
- אם הנך נוטה להיפצע ולדמם בקלות.
- אם הנך סובל מאנמיה.
- אם הנך נוטה לסבול מזיהומים.
- אם הנך סובל או סבלת בעבר מפרכוסים.
- אם הנך סובל מבעיות בתפקודי הכבד או הכליות, במיוחד אם אתה מטופל באמצעות דיאליזה.
- אם הנך סובל משלשולים.

אזהרות:

השימוש בזיבוקסיד עלול לגרום לגידול יתר במספר האורגניזמים שאינם רגישים לתרופה. אין להשתמש בתרופה זו לעיתים קרובות או לתקופה ממושכת בלי להיוועץ ברופא. בתקופת הטיפול בתרופה זו יש לערוך בדיקות דם, במיוחד בחולים שלוקחים תרופות שעלולות לגרום לירידה בספירת הטסיות ובתפקודן או בחולים הנוטלים לינזוליד יותר משבועיים. יש לערוך בדיקות ריאה בחולים הנוטלים את התרופה למשך תקופה ממושכת. אם הינך רגיש/ה למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפני נטילת התרופה.

אזהרות מיוחדות הנוגעות לשימוש בתרופה

- אם אתה רגיש למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפני נטילת התרופה.
- אין להיכנס להריון בתקופת הטיפול - יש להיוועץ ברופא על שימוש באמצעי מניעה נאותים.
- השימוש בזיבוקסיד עלול לגרום לגידול יתר במספר האורגניזמים שאינם רגישים לתרופה.
- אין להשתמש בתרופה זו לעיתים קרובות או לתקופה ממושכת בלי להיוועץ ברופא.
- בתקופת הטיפול בתרופה זו יש לערוך בדיקות דם, במיוחד בחולים שלוקחים תרופות שעלולות לגרום לירידה בספירת הטסיות ובתפקודן או בחולים הנוטלים לינזוליד יותר משבועיים.
- יש לערוך בדיקות ריאה בחולים הנוטלים את התרופה למשך תקופה ממושכת.

תגובות בין-תרופתיות:

אם הינך נוטל/ת תרופה נוספת, כולל תרופות הנמכרות ללא מרשם ותוספי תזונה, או אם גמרתי זה עתה טיפול בתרופה אחרת, עליך לדווח לרופא המטפל כדי למנוע סיכונים או אי-יעילות הנובעים מתגובות בין-תרופתיות, במיוחד לגבי תרופות מהקבוצות הבאות:

תרופות נגד דיכאון ומעכבי סרטונין, ריפמפיין.

תרופות נגד הצטננות או להקלה בגודש באף, המכילות פסודואפדרין, תרופות המכילות אפינפרין או דופמין (ראה פרק "מתי אין להשתמש בתרופה?").

אם אתה לוקח או לקחת לאחרונה תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.

במיוחד יש ליידע את הרופא לפני תחילת הטיפול אם אתה לוקח אחת מהתרופות הבאות:

- מפחיתי גודש (תכשירים לטיפול בשפעת והתקררות המכילים פסודואפדרין או פנילפרופאנולאמין).
 - תרופות לטיפול באסטמה כגון סאלבוטאמול, טרבוטאלין ופנוטרול.
 - תרופות לטיפול בדיכאון ממשפחת הטרזיקליים או חוסמי סרטונין סלקטיביים (SSRIs) כגון: אמטריפטילין, ציפרמיל, קלומיפראמין, דוסלפין, דוקספין, פלואוקסטין, פלובוקסאמין, אימיפראמין, לופראמין, פרוקסטין או סטרלין.
 - תרופות לטיפול במיגרנה כגון סומאטריפטאן וזולמיטריפטאן.
 - תרופות לטיפול בתגובה אלרגית חריפה כגון אדרנלין (אפינפריין).
 - תרופות העלולות להעלות את לחץ הדם כגון: נוראדרנלין (נוראפינפריין), דופמין ודובוטאמין.
 - תרופות לטיפול בכאב בינוני עד חמור כגון פתידין.
 - תרופות לטיפול בחרדה כגון בוספירון.
 - ריפאמפיצין – אנטיביוטיקה לטיפול בזיהום חיידקי.
- תרופות לדילול דם כגון ווארפריין.

מאחר והשילוב עם זיבוקסיד עלול להוביל להגברת תופעות לוואי כגון: שינויים בלחץ הדם, בחום הגוף או בקצב הלב. יתכן והרופא שלך ירצה לבדוק את מצב בריאותך הכללי ואת לחץ הדם שלך לפני ובמהלך הטיפול או יחליט כי טיפול אחר עדיף עבורך.

השימוש בתרופה ומזון

השימוש בתרופה עם או בלי אוכל. יש לבלוע את התרופה עם מעט מים. בתקופת הטיפול יש להמעיט באכילת מזון ובשתיית משקאות המכילים כמויות גבוהות של טירמין (Tyramine) כגון יין אדום, בירה, שמרים, סויה (כולל הרוטב) ומזונות שעברו תהליכי התססה, החמצה, עישון או יישון. זאת מאחר שבשילוב עם התרופה לחץ הדם עלול לעלות.

הריון והנקה

יש להיוועץ ברופא לפני התחלת הטיפול אם הנך בהריון או מניקה. יש להודיע לרופא מיד אם גילית כי את בהריון, יש חשד להריון או אם הנך מתכננת להיכנס להריון או להניק. זיבוקסיד עלול לפגוע בעובר ולכן אין להשתמש בתרופה בהריון אלא אם כן התועלת עולה על הסיכון. אין להניק במהלך הטיפול עם זיבוקסיד מאחר והתרופה עוברת לחלב האם ועלולה לפגוע בתינוק.

נהיגה ושימוש במכונות
השימוש בתרופה זו עלול לגרום לסחרחורות וטשטוש ראייה. אם זה קורה לך, אין לנהוג או להפעיל מכונות.

3. כיצד תשתמש בתרופה?

...
אסור לכתוש/לחצות/ללעוס! מכיוון שהטבלייה מצופה.

תופעות לוואי:
בנוסף לפעילות הרצויה של התרופה, בזמן השימוש בה עלולות להופיע השפעות לוואי כגון שלשול, בחילה/הקאות, כאב ראש; כאב בטן, נזירופתיה פריפרית, נזירופתיה אופטית הקשורה לעיתים לאיבוד ראייה, לקטיק אצידוזיס, טעם מתכתי, התכווצויות בבטן, פריחה, צביעה של הלשון ו/או השיניים.

תופעות לוואי המהיבות התייחסות מיוחדת:
שינויים בראייה כגון טשטוש בראייה, שינויים בספירת הדם, שלשולים חריפים (נדירות): המשך/ בטיפול ופנה/ לרופא מיד!
עוויתות (נדיר): הפסק הטיפול ופנה/ לרופא מיד!
בכל מקרה שבו הינך מרגיש/ה תופעות לוואי שלא צוינו בעלון זה, או אם חל שינוי בהרגשתך הכללית עליך להתייעץ עם הרופא מיד.

תופעות לוואי ותגובות בין תרופתיות בילדים:
על ההורים לדווח לרופא המטפל על כל תופעת לוואי וכן על כל תרופה נוספת הניתנת לילד/ה!
ראה/ לעיל תגובות בין-תרופתיות ותופעות לוואי מיוחדות שפורטו.

4. תופעות לוואי

כמו בכל תרופה, השימוש בתרופה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן

יש להפסיק את השימוש ולפנות מיד לרופא במקרה של:

- הופעת סימנים של תגובה אלרגית חריפה כגון: תופעות עוריות הכוללות אדמומיות וכאב, קשקשים (דרמטיטיס), פריחה, גרד, שלפוחיות על העור, נפיחות בעיקר באזור הפנים, בלשון או בגרון, קושי בבליעה, וקשיי נשימה.
- הופעת שלשול שהופך לחמור או שאינו חולף, או במידה והנך מבחין בדם או ריר בצואה, יש להפסיק את הטיפול מיד ולפנות לרופא. במצב זה, אין לקחת תרופות להאטת או עצירת פעילות מעיים. לעיתים נדירות תופעה זו יכולה להפוך למסכנת חיים.

יש לפנות לרופא מיד במקרה של:

- הופעת הפרעות בראייה כגון: טשטוש ראייה, שינויים בראיית צבעים, קושי בהבחנה בפרטים או צמצום שדה הראייה.
- אם הנך סובל מבחילות או הקאות חוזרות, כאבי בטן או נשימה מואצת
- אם הנך מאבד את התחושה, או מרגיש עקצוץ או דקירות, בזרועות או ברגליים.
- אם הנך חווה פרכוסים, רעידות, נוקשות שרירים, בעיות בקואורדינציה, בלבול, הזיות במיוחד אם הנך נוטל במקביל תרופות לטיפול בדיכאון מקבוצת חוסמי סרטונין סלקטיביים (SSRIs).
- איבוד התחושה והעקצוץ בגפיים וכן טשטוש ראייה, דווחו על ידי מטופלים שקיבלו את התרופה במשך יותר מ-28 יום.

תופעות לוואי נוספות

תופעות לוואי המופיעות לעיתים קרובות:

- זיהום פטרייתי, בעיקר בפה או בנרתיק.
- כאבי ראש
- טעם מתכתי בפה
- הפרעות בעיכול, כאבי בטן, שלשולים, עצירות, בחילות או הקאות
- שינויים בתוצאות בדיקות דם (כולל בדיקות לתפקוד הכבד או הכליות ובדיקות לרמות סוכר בדם).
- נטייה מוגברת לחבלות ודימומים, תיתכן ירידה בתאי דם מסוימים אשר תגרום לבעיות בקרישת הדם או לאנמיה.
- הפרעות בשינה
- עליה בלחץ דם
- שינויים ברמות תאי דם שונים העלולים להשפיע על יכולת מערכת החיסון לעמוד מול זיהומים.
- פריחה ו/או גרד בעור
- סחרחורות
- כאב ממוקד
- חום

תופעות לוואי המופיעות לעיתים רחוקות:

- זיהומים בנרתיק או באזור איברי המין הנשיים
- תחושת עקצוץ או נימול
- טשטוש ראייה
- צלצולים באוזניים
- דלקת ורידים

- כאב או יובש בפה, נפיחות, כאב או שינוי צבע בלשון
- תכיפות במתן שתן
- רעידות
- תחושת עייפות או צמא
- דלקת בלבלב
- הזעה מוגברת
- שינויים בבדיקות דם לתפקוד הכבד או בכליות
- עוויתות
- רמות נמוכות של נתרן בדם
- כשל כליתי
- ירידה ברמת טסיות הדם
- נפיחות בבטן
- אירוע מוחי חולף (הפרעה זמנית בזרימת הדם למח, הגורמת לתסמינים זמניים כגון: איבוד ראייה, חולשה בזרועות או ברגליים, הפרעות בדיבור ואיבוד הכרה)
- דלקת בעור
- עלייה ברמות קראטינין
- כאב בקיבה
- שינויים בקצב לב

תופעות לוואי המופיעות לעיתים נדירות:

- צמצום שדה בראייה
- שינויי שטחי בצבע השיניים (ניתן להסרה בניקוי שיניים ע"י איש מקצוע)

תופעות לוואי אשר שכיחות אינה ידועה:

- סינדרום סרטונין (התסמינים לכך יכולים לכלול: קצב לב מהיר, בלבול, הזעה מוגברת, הזיות ורעידות לא נשלטות)
- עלייה ברמת החומציות בגוף (Lactic acidosis) התסמינים לכך יכולים לכלול בחילות והקאות חוזרות, כאב בטני ונשימה מואצת)
- בעיות חמורות בעור
- אנמיה סידרובלסטית
- נשירת שיער
- שינויים בראיית צבעים, קושי בהבחנה בפרטים
- ירידה בספירת דם
- חולשה ושינויים בתחושה

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא. ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי, או ע"י כניסה לקישור: <https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

5. איך לאחסן את התרופה?

מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא. אין להשתמש בתרופה אחרי תאריך התפוגה ((exp. date) המופיע על גבי האריזה. תאריך התפוגה מתייחס ליום האחרון של אותו חודש. יש לאחסן בטמפרטורה מתחת ל- 25°C. יש להגן מאור.

6. מידע נוסף

כיצד נראית התרופה ומה תוכן האריזה :

זיבוקסיד: טבליה לבנה בצורת אליפסה שעליה מוטבע באדום "ZYVOXID 600".

בעל הרישום: פייזר פי אף אי פרמצבטיקה ישראל בע"מ, שנקר 9, הרצליה פיתוח 46725.

העלונים המעודכנים נשלחו למשרד הבריאות לצורך פרסומם במאגר התרופות שבאתר משרד הבריאות: <https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h>

לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פרמצבטיקה ישראל בע"מ שנקר 9, ת.ד. 12133, הרצליה פיתוח, 46725.

בברכה,
קלאורה שירן
רוקחת ממונה