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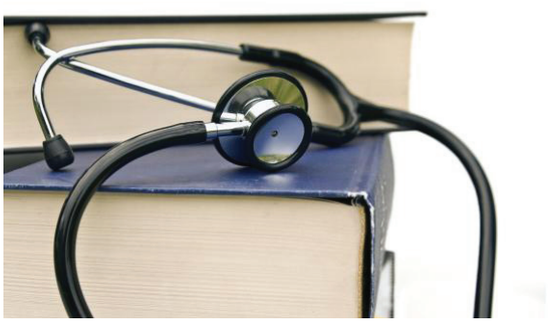

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Emergency Ultrasound Fellowship

HEALTH SCIENCES NORTH, SUDBURY, ONTARIO

2013–2014 Academic Year

Applications are invited for the position of **Emergency Ultrasound Fellow**. Sudbury's emergency physicians have been performing emergency ultrasound since 2001. Sudbury is the base for the Emergency Department Echo courses. EDE 1 has taught "EDE" to over 6000 physicians worldwide. The EDE 2 (Advanced) Course made its debut in 2009. Our emergency department is recognized as a training centre by the Canadian Emergency Ultrasound Society (CEUS), and has welcomed dozens of emergency physicians from across the country for CEUS independent practitioner training. Emergency ultrasound is an integral part of the curriculum of Sudbury's CFPC(EM) residency – one of the largest in the country. Sudbury is the East Campus of the Northern Ontario School of Medicine. The Sudbury ED has one of the highest volumes and acuities in Ontario. Health Sciences North is the Trauma and Tertiary Care Centre for Northeastern Ontario.

The fellow will develop expert skills in basic and advanced emergency ultrasound. Valuable experience in education and research will be gained. The fellow will have the opportunity to become an instructor with the EDE courses, as well as a CEUS instructor. The main objective of the one-year fellowship is to train future leaders in emergency ultrasound in Canada.

Applicants must be certified in emergency medicine (FRPC(C), CFPC(EM), or ABEM) or in their final year of emergency medicine residency. FRCP residents in the latter half of residency will be considered for a 6-12 month rotation on a case-by-case basis. Applicants must be eligible for Ontario licensure. Interested candidates should submit a letter and CV no later than Jan 15, 2013. To submit an application or for further information, please contact:

Steve Socransky, MD, FRCPC, ABEM, CEUS
Ray Wiss, MD, CSPQ, CFPC(EM), CEUS
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Health Sciences North
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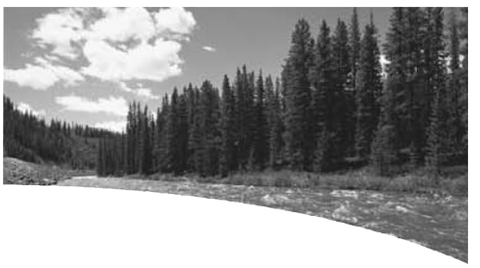

FULL TIME POSITIONS

CALGARY EMERGENCY DEPARTMENT

The Department of Emergency Medicine (Alberta Health Services – Calgary) is now accepting applications for FULL TIME EMERGENCY PHYSICIANS. Flexible start dates are available, beginning in January 2012.

The Calgary Department of Emergency Medicine encompasses two emergency medicine residency programs and three hospital sites seeing over 200,000 patients per year. A fourth hospital site, the South Health Campus will be opening in Summer 2012. In addition to a full spectrum of high acuity clinical medicine, trauma and cardiac care, we have active programs in human patient simulation and EM ultrasound, and Calgary is the home of STARS (Shock Trauma Air Rescue Society), one of North America's longest operating rotary wing aero medical systems. The Calgary Department of Emergency Medicine has a growing academic program with research and teaching opportunities.

Calgary is a vibrant, multicultural city (population 1.2 million) near the Rocky Mountains, Banff National Park and Lake Louise with a full range of recreational, sports and cultural opportunities.

Alberta emergency physicians are among the highest paid in North America, and enjoy a flexible work/life balance while working is a highly supportive, collegial environment.

Requirements: CCFP (EM), ABEM or FRCPC certification is required, as well as eligibility for licensure in the province of Alberta.

Interested applicants should forward their curriculum vitae, cover letter and have 3 letters of recommendation sent to:

Scott H. Banks, MBA, CHRP, CITP
Zone Department Manager, Emergency Medicine
Foothills Medical Centre
Room C231, 1403 -29th St NW
Calgary, AB T2N 2T9

Email: scott.banks@albertahealthservices.ca

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Pr CYANOKIT® 5 g
HYDROXOCOBALAMIN

PRESCRIBING SUMMARY

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Antidote (Powder for solution for infusion)

INDICATIONS AND CLINICAL USE: Cyanokit® contains hydroxocobalamin, an antidote indicated for the treatment of known or suspected cyanide poisoning. Cyanokit® is to be administered together with appropriate decontamination and supportive measures.

Identifying patients with cyanide poisoning: Cyanide poisoning may result from inhalation, ingestion, or dermal exposure to various cyanide containing compounds, including smoke from closed space fires. Sources of cyanide poisoning include hydrogen cyanide and its salts, cyanogens, including cyanogenic plants, aliphatic nitriles, or prolonged exposure to sodium nitroprusside. The presence and extent of cyanide poisoning are often initially unknown. There is no widely available, rapid, confirmatory cyanide blood test. Treatment decisions must be made on the basis of clinical history and signs and symptoms of cyanide intoxication. If clinical suspicion of cyanide poisoning is high, Cyanokit® should be administered without delay.

Table 1. Common Signs and Symptoms of Cyanide Poisoning

Symptoms	Signs
• Headache	• Altered Mental Status (e.g., confusion, disorientation)
• Confusion	• Seizures or Coma
• Dyspnea	• Mydriasis
• Chest tightness	• Tachypnea/Hyperpnea (early)
• Nausea	• Bradypnea/Apnea (late)
	• Hypertension (early)/Hypotension (late)
	• Cardiovascular collapse
	• Vomiting
	• Plasma lactate concentration ≥8 mmol/L

In some settings, panic symptoms, including tachypnea and vomiting, may mimic early cyanide poisoning signs. The presence of altered mental status (confusion and disorientation) and/or mydriasis is suggestive of true cyanide poisoning, although these signs can occur with other toxic exposures as well.

Smoke inhalation: Not all smoke inhalation victims will necessarily have cyanide poisoning, and may present with burns, trauma, and exposure to additional toxic substances making a diagnosis of cyanide poisoning particularly difficult. Prior to the administration of Cyanokit,® smoke-inhalation victims should be assessed for the following:

- exposure to fire smoke in an enclosed area
- soot present around mouth, nose and/or oropharynx
- altered mental status

Use with Other Cyanide Antidotes: The safety of administering other cyanide antidotes simultaneously with Cyanokit® has not been established. If the decision is made to administer another cyanide antidote with Cyanokit,® these medicinal products must not be administered concurrently in the same intravenous line (see **DOSAGE AND ADMINISTRATION**).

Geriatrics (≥ 65 years of age): Approximately 50 known or suspected cyanide victims aged 65 or older received hydroxocobalamin in clinical studies. In general, the safety and effectiveness of hydroxocobalamin in these patients was similar to that of younger patients. No adjustment of dose is required in elderly patients.

Pediatrics (< 18 years of age): Limited safety and efficacy data are available for pediatric patients. In infants to adolescents, the dose of Cyanokit® is 70 mg/kg (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS: None.

SPECIAL POPULATIONS: For use in special populations, see **WARNINGS AND PRECAUTIONS**, Special Populations.

Safety Information

WARNINGS AND PRECAUTIONS

General: Emergency Patient Management – In addition to Cyanokit,® treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of any seizure activity. Consideration should be given to decontamination measures based on the route of exposure. Cyanokit® does not substitute for oxygen therapy and must not delay the set up of the above measures.

Cardiovascular: Transient, generally asymptomatic, increase in blood pressure may occur in patients receiving hydroxocobalamin. The maximal increase in blood pressure has been observed toward the end of infusion.

Immune: Known hypersensitivity to hydroxocobalamin or vitamin B_{12} must be taken into benefit-risk consideration before administration of Cyanokit,® since hypersensitivity reactions may occur in patients receiving hydroxocobalamin. Allergic reaction may include anaphylaxis, chest tightness, edema, urticaria, pruritus, dyspnea and rash.

Renal: Based on its vasopressor effect, hydroxocobalamin may cause vasoconstriction of the renal vasculature. Since no more than two injections of hydroxocobalamin are to be administered it is unlikely that this will have any effect in patients with normal renal function; the outcome in patients with impaired renal function is unknown.

Sexual Function/Reproduction: No animal studies on male and female fertility and early embryonic development to implantation have been performed. Developmental toxicity including teratogenicity was observed in animal studies at doses that correspond approximately to the maximum recommended human dose (see **TOXICOLOGY**). Hydroxocobalamin levels were detected in urine for some patients up to 35 days following treatment with Cyanokit® indicating that elimination of Cyanokit® from the body may not be completed after 35 days. Based on these data, it is recommended to practice adequate methods of contraception for 2 months following Cyanokit® treatment.

Skin: Photosensitivity – Hydroxocobalamin absorbs visible light in the UV spectrum. It therefore has potential to cause photosensitivity. While it is not known if the skin redness predisposes to photosensitivity, patients should be advised to avoid direct sun while their skin remains discoloured.

Special Populations

Pregnant Women: Animal studies have shown teratogenic effects following daily exposure throughout organogenesis (see **TOXICOLOGY**). There are no adequate and well-controlled studies in pregnant women. However, treatment of maternal/fetal cyanide poisoning may be life-saving. The effect of Cyanokit® on labour and delivery is unknown.

Nursing Women: It is not known whether hydroxocobalamin is excreted in human milk. Because of the unknown potential for adverse reactions in nursing infants, discontinue nursing after Cyanokit® treatment.

Renal Impairment: The safety and effectiveness of Cyanokit® have not been studied in patients with renal impairment. Hydroxocobalamin and cyanocobalamin are eliminated unchanged by the kidneys. Oxalate crystals have been observed in the urine of both healthy subjects given hydroxocobalamin and patients treated with hydroxocobalamin following suspected cyanide poisoning.

Hepatic Impairment: The safety and effectiveness of Cyanokit® have not been studied in patients with hepatic impairment.

Monitoring and Laboratory Tests

Effects on blood cyanide assay: Hydroxocobalamin will lower blood cyanide concentrations. While determination of blood cyanide concentration is not required and must not delay treatment with hydroxocobalamin, it may be useful for documenting cyanide poisoning. If a cyanide blood level determination is planned, it is recommended to draw the blood sample before initiation of treatment with Cyanokit.®

Interference with burn assessment: Because of its deep red colour, hydroxocobalamin has the potential to induce a red colouration of the skin and therefore may interfere with burn assessment. However, skin lesions, edema, and pain are highly suggestive of burns.

Interference with laboratory tests: Because of its deep red colour, hydroxocobalamin has the potential to interfere with determination of laboratory parameters (e.g., clinical chemistry, hematology, coagulation, and urine parameters) (Table 2). In vitro tests indicate that the extent and duration of the interference is dependent on numerous factors such as the dose of hydroxocobalamin, analyte, analyte concentration,

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methodology, analyzer, concentrations of cobalamins-(III) including cyanocobalamin and partially the time between sampling and measurement. Based on in vitro studies and pharmacokinetic data obtained in healthy volunteers the following table describes interference with laboratory tests that may be observed following a 5 g dose of hydroxocobalamin. Interference following a 10 g dose can be expected to last up to an additional 24 hours. The extent and duration of interference in cyanide-poisoned patients may differ according to the severity of intoxication. Results may vary considerably from one analyzer to another, therefore, caution is required when reporting and interpreting laboratory results.

Table 2. Laboratory Interference Observed with in vitro Samples of Hydroxocobalamin

Laboratory Parameter	No Interference Observed	Artificially Increased[a]	Artificially Decreased[a]	Unpredictable[c]	Duration of Interference
Clinical Chemistry	Calcium Sodium Potassium Chloride Urea Gamma glutamyl transferase (GGT)	Creatinine Total and conjugate bilirubin[b] Triglycerides Cholesterol Total protein Glucose Albumin Alkaline phosphatase	Alanine aminotransferase (ALT) Amylase	Phosphate Uric Acid Aspartate aminotransferase (AST) Creatine Kinase (CK) Creatine Kinase isoenzyme MB (CKMB) Lactate dehydrogenase (LDH)	24 hours with the exception of bilirubin (up to 4 days)
Hematology	Erythrocytes Hematocrit Mean corpuscular volume (MCV) Leukocytes Lymphocytes Monocytes Eosinophils Neutrophils Platelets	Hemoglobin (Hb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Basophils			12 – 6 hours
Coagulation				Activated partial thromoplastin time (aPTT) Prothrombin time (PT) Quick or INR	24 – 48 hours
Urinalysis		pH (with doses ≥ 5 g) Glucose Protein Erythrocytes Leukocytes Ketones Bilirubin Urobilinogen Nitrite	pH (with equivalent doses of < 5 g)		48 hours up to 8 days; colour changes may persist up to 28 days

[a] ≥ 10% interference observed on at least 1 analyzer
[b] Artificially decreased using the diazo method
[c] Inconsistent results
Analyzers used: ACL Futura (Instrumentation Laboratory), AxSYM®/Architect™ (Abbott), BM Coasys[110] (Boehringer Mannheim), CellDyn 3700® (Abbott), Clinitek® 500 (Bayer), Cobas Integra® 700, 400 (Roche), Gen-S Coultronics, Hitachi 917, STA® Compact, Vitros® 950 (Ortho Diagnostics).

Interference with hemodialysis machines: Because of its deep red colour, hydroxocobalamin may cause hemodialysis machines to shut down due to an erroneous detection of a 'blood leak'. This should be considered before hemodialysis is initiated in patients treated with hydroxocobalamin.

ADVERSE REACTIONS (see **Supplemental Product Information** for full listing): **Adverse Drug Reaction Overview:** Serious adverse reactions with hydroxocobalamin include allergic reactions and increases in blood pressure (see **WARNINGS AND PRECAUTIONS**). A total of 347 subjects were exposed to hydroxocobalamin in clinical studies. Of these 347 subjects, 245 patients had suspected exposure to cyanide at the time of hydroxocobalamin administration. The remaining 102 subjects were healthy volunteers who had not been exposed to cyanide at the time of hydroxocobalamin administration. Most patients will experience a reversible red colouration of the skin and mucous membranes that may last up to 15 days after administration of Cyanokit.® All patients will show a dark red colouration of the urine that is quite marked during the three days following administration. Urine colouration may last up to 35 days after administration of Cyanokit.®

Post-Market Adverse Drug Reactions: The following adverse events have been reported in post-marketing surveillance. The relationship of these events to Cyanokit® use is not known. Smoke inhalation and cyanide exposure may have contributed to these events: abnormal laboratory tests, pulmonary edema, cardiac arrest, renal failure – in some cases requiring dialysis, and transient impairment of renal function. To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug, you may notify Health Canada by toll-free telephone: 1-866-234-2345.

DRUG INTERACTIONS (also see **Supplemental Product Information**): **Overview:** Due to its high molecular weight, hydroxocobalamin is unlikely to interact with or inhibit CYP450 enzymes at clinically relevant concentrations. It is therefore considered to have low potential to be involved in drug-drug interactions with drugs that are substrates of CYP450. Physical incompatibility (particle formation) and chemical incompatibility were observed with the mixture of hydroxocobalamin in solution with selected drugs that are frequently used in resuscitation efforts. Hydroxocobalamin is also chemically incompatible with sodium thiosulfate and sodium nitrite and has been reported to be incompatible with ascorbic acid. Therefore, these and other drugs should not be administered simultaneously through the same IV line as hydroxocobalamin (see **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: No formal drug-drug interaction studies with hydroxocobalamin have been done.

Drug-Food Interactions: No formal drug-food interaction studies with hydroxocobalamin have been done.

Administration

DOSAGE AND ADMINISTRATION: Dosing Considerations: Comprehensive treatment of acute cyanide intoxication requires support of vital functions. Cyanokit® should be administered in conjunction with appropriate airway, ventilatory and circulatory support. The safety of administering other cyanide antidotes simultaneously with Cyanokit® has not been established. If the decision is made to administer another cyanide antidote with Cyanokit,® these medicinal products must not be administered simultaneously through the same intravenous line.

Recommended Dose and Dosage Adjustment: In adults, the initial dose of Cyanokit® is 5 g administered as an IV infusion. Depending on the severity of the poisoning and the clinical response, a second dose may be administered by IV infusion. The maximum recommended total dose is 10 g. In infants and adolescents, the initial dose of Cyanokit® is 70 mg/kg body weight not exceeding 5 g. Depending on the severity of the poisoning and the clinical response, a second dose may be administered by IV infusion. The maximum recommended total dose is 140 mg/kg body weight not exceeding 10 g (Table 3).

Table 3. Initial Dosing Guidelines in Infants and Adolescents

Body weight in kg	5	10	20	30	40	50	60
Initial dose in g	0.35	0.70	1.40	2.10	2.80	3.50	4.20
Initial dose in mL	14	28	56	84	112	140	168

Use in Renal and Hepatic Impairment: Although the safety and efficacy of hydroxocobalamin has not been studied in patients with renal or hepatic impairment, Cyanokit® is administered as emergency therapy in an acute, life-threatening situation only, and no dosage adjustment is required in these patients.

Administration: The initial dose of hydroxocobalamin for adults is 5 g (i.e., two 2.5 g vials or one 5 g vial) administered as an intravenous (IV) infusion over 15 minutes (approximately 15 mL/min). Depending upon the severity of the poisoning and the

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clinical response, a second dose of 5 g may be administered by IV infusion for a total dose of 10 g. The rate of infusion for the second dose ranges from 15 minutes (for patients who are extremely unstable) to 2 hours depending on the patient's condition.

Table 4. Reconstitution

Dose per Vial	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
2.5 g	100 mL	Approx. 100 mL	25 mg/mL
5 g	200 mL	Approx. 200 mL	25 mg/mL

2.5g Vial: Each 2.5 g vial is to be reconstituted with 100 mL of diluent using the supplied sterile transfer device. Sodium chloride 9 mg/mL (0.9%) solution for injection is the recommended diluent. Only when sodium chloride 9 mg/mL (0.9%) solution for injection is not available, Lactated Ringer solution or 5% glucose can also be used. The Cyanokit® 2.5 g vial is to be rocked or inverted for at least 30 seconds to mix the solution. It must not be shaken as shaking the vial may cause foam and therefore may make checking reconstitution less easy.

5 g Vial: Each 5 g vial is to be reconstituted with 200 mL of diluent using the supplied sterile transfer device. Sodium chloride 9 mg/mL (0.9%) solution for injection is the recommended diluent. Only when sodium chloride 9 mg/mL (0.9%) solution for injection is not available, Lactated Ringer solution or 5% glucose can also be used. The Cyanokit® 5 g vial is to be rocked or inverted for at least 60 seconds to mix the solution. It must not be shaken as shaking the vial may cause foam and therefore may make checking reconstitution less easy. Because the reconstituted solution is a dark red solution, some insoluble particles may not be seen. The intravenous infusion set provided in the kit must therefore be used as it includes an appropriate filter and is to be primed with the reconstituted solution. Repeat this procedure if necessary with the second vial.

Incompatibility Information: Physical incompatibility (particle formation) and chemical incompatibility were observed with the mixture of hydroxocobalamin in solution with selected drugs that are frequently used in resuscitation efforts. Hydroxocobalamin is also chemically incompatible with sodium thiosulfate and sodium nitrite and has been reported to be incompatible with ascorbic acid. Therefore, these and other drugs must not be administered simultaneously through the same IV line as hydroxocobalamin. Simultaneous administration of hydroxocobalamin and blood products (whole blood, packed red cells, platelet concentrate and/or fresh frozen plasma) through the same IV line is not recommended. However, blood products and hydroxocobalamin can be administered simultaneously using separate IV lines (preferably on contralateral extremities, if peripheral lines are being used).

Storage of Reconstituted Drug Product: Once reconstituted, hydroxocobalamin is stable for up to 6 hours at a temperature between 2°C and 40°C (35.6°F and 104°F). Do not freeze. Any reconstituted product not used by 6 hours should be discarded.

Supplemental Product Information

ADVERSE REACTIONS: Systematic collection of adverse events was not done in all clinical studies involving known or suspected cyanide-poisoning victims who were treated with hydroxocobalamin. The interpretation of causality in these studies is limited due to lack of a control group and due to circumstances of administration (e.g., use in fire victims).

Clinical Trial Adverse Drug Reactions: *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Experience in Healthy Subjects: A double-blind, randomized, placebo-controlled, single-ascending dose (2.5, 5, 7.5, and 10 g) study was conducted to assess the safety, tolerability, and pharmacokinetics of hydroxocobalamin in 136 healthy adult subjects. Because of the dark red colour of hydroxocobalamin, the two most frequently occurring adverse reactions were chromaturia (red-coloured urine) which was reported in all subjects receiving a 5 g dose or greater; and erythema (skin redness), which occurred in most subjects receiving a 5 g dose or greater. Adverse reactions reported in at least 1% of the 5 g dose group and corresponding rates in the 10 g and placebo groups are shown in Table 5.

Table 5. Incidence of Adverse Reactions Occurring in ≥ 1% of Healthy Subjects in 5 g Dose Group and Corresponding Incidence in 10 g Dose Group and Placebo

	5 g Dose Group		10 g Dose Group	
	Hydroxo-cobalamin	Placebo	Hydroxo-cobalamin	Placebo
	N = 66	N = 22	N = 18	N = 6
Adverse Drug Reaction	n (%)	n (%)	n (%)	n (%)
Eye disorder				
Eye redness	2 (3)	0	1 (6)	0
Renal and Urinary Disorders				
Chromaturia (red coloured urine)	66 (100)	0	18 (100)	0
Pollakiuria (frequent urination)	1 (2)	0	0	0
Skin and subcutaneous tissue Disorders				
Erythema	62 (94)	0	18 (100)	0
Rash*	14 (21)	0	3 (17)	0
Immune Disorders				
Face edema	1 (2)	0	0	0
Pruritus	1 (2)	0	3 (17)	0
Urticaria	1 (2)	0	0	0
Investigations				
Blood amylase increased	1 (2)	0	0	0
Blood pressure increased	12 (18)	0	5 (28)	0
Lymphocyte percent decreased	5 (8)	0	3 (17)	0
Gastrointestinal disorders				
Abdominal discomfort	2 (3)	0	2 (11)	0
Flatulence	1 (2)	0	0	0
Loose stools	1 (2)	0	0	0
Nausea	4 (6)	1 (5)	2 (11)	0
Vomiting	2 (3)	0	0	0
Nervous System Disorders				
Dizziness	2 (3)	0	1 (6)	0
Headache	4 (6)	1 (5)	6 (33)	0
General disorders and administrative site conditions				
Chest discomfort	3 (5)	0	2 (11)	0
Discomfort	1 (2)	0	0	0
Feeling hot and/or cold	2 (3)	0	0	0
Infusion site reaction	4 (6)	0	7 (39)	0
Musculoskeletal and connective tissue disorders				
Joint/back pain	2 (3)	0	0	0
Psychiatric disorders				
Restlessness	2 (3)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Dyspnea	1 (2)	0	0	0
Sore or dry throat	3 (5)	0	3 (17)	0

* Rashes were predominately acneiform

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Less Common Adverse Drug Reactions Occurring at a rate of less than 1%

Eye disorders: Swelling, irritation.

Gastrointestinal disorders: Dyspepsia, diarrhea, dysphagia, hematochezia.

General disorders and administration site conditions: Peripheral edema.

Immune system disorders: Allergic reactions including angioneurotic edema and skin eruption (see **WARNINGS AND PRECAUTIONS**).

Nervous system disorders: Memory impairment.

Respiratory, thoracic and mediastinal disorders: Pleural effusion.

Vascular disorders: Hot flush.

Experience in Known and Suspected Poison Victims: Four open-label, uncontrolled, clinical studies (one of which was prospective and three of which were retrospective) were conducted in known or suspected cyanide-poisoning victims. A total of 245 patients received hydroxocobalamin treatment in these studies. Systematic collection of adverse events was not done in all of these studies and interpretation of causality is limited due to the lack of a control group and due to circumstances of administration (e.g., use in fire victims). Adverse reactions reported in these studies listed by system organ class included:

Cardiac disorders: Ventricular extrasystoles, an increase in heart rates, electrocardiogram repolarization abnormality.

Adverse reactions common to both the studies in known or suspected cyanide poisoning victims and the study in healthy volunteers are listed in the healthy volunteer section of the Product Monograph only and are not duplicated in this list.

Abnormal Hematologic and Clinical Chemistry Findings: Cyanokit® may cause red discolouration of the plasma, which may cause artificial elevation or reduction in the levels of certain laboratory parameters (see **WARNINGS AND PRECAUTIONS**). White blood cell counts (WBC) showed a slight and transient increase in mean values from baseline at 2 to 12 hours after treatment in healthy subjects, and small decreases in serum sodium levels were also observed. Changed values generally remained within normal ranges. Other minor and transient changes in hematology and clinical chemistry findings were considered due to interference by hydroxocobalamin or due to individual variation.

DRUG INTERACTIONS: Drug-Herb Interactions: Interactions with herbal products have not been established.

Drug-Laboratory Interactions: Because of its deep red colour, hydroxocobalamin has been found to interfere with colourimetric determination of certain laboratory parameters (e.g., clinical chemistry, hematology, coagulation, and urine parameters). In vitro tests indicated that the extent and duration of the interference are dependent on numerous factors such as the dose of hydroxocobalamin, analyte, methodology, analyzer, hydroxocobalamin concentration, and partially on the time between sampling and measurement. Based on in vitro studies and pharmacokinetic data obtained in healthy volunteers, Table 2 describes laboratory interference that may be observed following a 5 g dose of hydroxocobalamin (see **WARNINGS AND PRECAUTIONS**). Interference following a 10 g dose can be expected to last up to an additional 24 hours. The extent and duration of interference in cyanide-poisoned patients may differ. Results may vary substantially from one analyzer to another; therefore, caution should be used when reporting and interpreting laboratory results.

OVERDOSAGE:

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

Limited data are available about overdose with Cyanokit® Doses as high as 15 g have been administered without reported specific dose related adverse reactions. If overdose occurs, treatment is directed to the management of symptoms. Hemodialysis may be effective in such a circumstance, but is only indicated in the event of significant hydroxocobalamin-related toxicity. Because of its deep red colour, hydroxocobalamin may interfere with the performance of hemodialysis machines (see **WARNINGS AND PRECAUTIONS**, Monitoring and Laboratory Tests).

Product Monograph available on request.

References: 1. CYANOKIT® (Hydroxocobalamin) Product Monograph, EMD Serono, October, 2011.

Member PAAB R&D

Importer & Distributor of Cyanokit®:
EMD Serono, A Division of EMD Inc., Canada
2695 North Sheridan Way, Suite 200
Mississauga, Ontario L5K 2N6 Canada
www.emdserono.ca
An affiliate of Merck KGaA, Darmstadt, Germany

EMD Serono

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IV/Oral

Pr ZYVOXAM® (linezolid)

PRESCRIBING SUMMARY

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Antibacterial Agent

INDICATIONS AND CLINICAL USE: ZYVOXAM Tablets, Injection and Oral Suspension are indicated for: treatment of adult patients with the following infections, when caused by susceptible strains of the designated aerobic Gram-positive micro-organisms below.

Note: ZYVOXAM is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see **WARNINGS AND PRECAUTIONS**).

Vancomycin-Resistant *Enterococcus faecium* (VREF) Infections: ZYVOXAM is indicated for the treatment of the following infections when due to VREF: intra-abdominal, skin and skin-structure and urinary tract infections (including cases associated with concurrent bacteremia). Note: This indication for VREF is based on non-comparative studies.

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains only).

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible strains only) including cases with concurrent bacteremia or *Staphylococcus aureus* (methicillin-susceptible and -resistant strains).

Complicated skin and skin structure infections, including non-limb threatening diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes* or *Streptococcus agalactiae*.

Note: ZYVOXAM has not been studied in the treatment of necrotizing fasciitis or decubitus ulcers.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

Prior to instituting treatment with ZYVOXAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to ZYVOXAM. In infections where concomitant Gram-negative and/or anaerobic pathogens are suspected or are known to be present, ZYVOXAM must be used in combination with an appropriate antibiotic in order to provide adequate antimicrobial coverage. If clinically indicated, treatment with ZYVOXAM may be started empirically before results of susceptibility testing are available. Local epidemiology and susceptibility patterns may help in the selection of empiric therapy. Once culture results become available, antimicrobial therapy can be adjusted accordingly. To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOXAM and other antibacterial drugs, ZYVOXAM should be used only to treat infections that are proved or suspected to be caused by susceptible bacteria. Because the inappropriate use of antibiotics can increase organism resistance, prescribers should carefully consider alternatives before initiating treatment with ZYVOXAM in an outpatient setting.

CONTRAINDICATIONS: ZYVOXAM Tablets, Injection and Oral Suspension are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

Monoamine Oxidase Inhibitors: ZYVOXAM 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 (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Potential Interactions Producing Elevation of Blood Pressure: Unless patients are monitored for potential increases in blood pressure, ZYVOXAM should not be administered to patients with uncontrolled hypertension, pheochromocytoma or 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 **DRUG INTERACTIONS, Drug-Drug Interactions**).

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 **DRUG INTERACTIONS, Drug-Drug Interactions**).

Safety Information

WARNINGS AND PRECAUTIONS

General: The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. ZYVOXAM Tablets, Injection and Oral Suspension have not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome or untreated hyperthyroidism. Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOXAM (see **ADVERSE REACTIONS, DRUG INTERACTIONS, Drug-Food Interactions** for foods or beverages with high tyramine content). The safety and efficacy of ZYVOXAM given for longer than 28 days have not been evaluated in controlled clinical trials.

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

Drug Interactions (see also **DRUG INTERACTIONS, Drug-Drug Interactions**)

Serotonin Syndrome: Very rare spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic agents have been reported. Since there is limited experience with concomitant administration of linezolid and serotonergic agents (such as serotonin re-uptake inhibitors, tricyclic antidepressants and serotonin 5-HT1 receptor agonists), 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 (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Drug-Drug Interactions, Serotonergic Agents**).

Carcinogenesis and Mutagenesis (see **TOXICOLOGY, Carcinogenicity, Toxicology** and **Mutagenicity**).

Gastrointestinal: *Clostridium difficile*-associated disease (CDAD) has been reported with use of many antibacterial agents, including ZYVOXAM. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth to *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

Hematologic: Myelosuppression (anemia including pure red blood cell aplasia, leucopenia, 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 at least weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, patients who are at increased risk for bleeding, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or decreased hemoglobin levels or platelet counts or function, 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.

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Neurologic: Peripheral neuropathy has been reported primarily in patients treated for longer than the maximum recommended duration of 28 days with ZYVOXAM. When outcome was known, recovery was reported in only some cases following ZYVOXAM withdrawal. If symptoms of peripheral neuropathy such as numbness, tingling, prickling sensations or burning pain occur, the continued use of ZYVOXAM should be weighed against the potential risk. Convulsions have been reported to occur rarely in patients when treated with ZYVOXAM. In most of these cases, a history of seizures or risk factors for seizures was reported.

Ophthalmologic: Optic neuropathy has been reported in patients treated with ZYVOXAM, primarily those treated for longer than the maximum recommended duration of 28 days. When outcome was known, recovery was reported in some cases following ZYVOXAM withdrawal. In cases of optic neuropathy that progressed to loss of vision, patients were treated for longer than the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOXAM for <28 days. **Visual function should be monitored in all patients taking ZYVOXAM for longer than the maximum recommended duration and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOXAM.** If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision or visual field defect, prompt ophthalmologic evaluation is recommended. If optic neuropathy occurs, the continued use of ZYVOXAM in these patients should be weighed against the potential risks.

Special Populations: Pregnant Women: There are no adequate and well-controlled studies in pregnant women. ZYVOXAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: ZYVOXAM and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOXAM is administered to a nursing woman.

Pediatrics: There are insufficient data on the safety and efficacy of linezolid in children and adolescents (<18 years old) to establish dosage recommendations (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics** in the Product Monograph). Therefore, until further data are available, use of linezolid in this age group is not recommended.

Geriatrics: Of the 2046 patients treated with ZYVOXAM in phase III comparator-controlled clinical trials, 589 (29%) were ≥65 years and 253 (12%) were ≥75 years. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Monitoring and Laboratory Tests: Complete blood counts should be monitored at least weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, patients who are at increased risk for bleeding, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or decreased hemoglobin levels or platelet counts or function, or those with a chronic infection who have received previous or concomitant antibiotic therapy (see **WARNINGS AND PRECAUTIONS, Hematologic: Myelosuppression**). **Visual function should be monitored in all patients taking ZYVOXAM for longer than the maximum recommended duration and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOXAM**. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision or visual field defect, prompt ophthalmologic evaluation is recommended (see **WARNINGS AND PRECAUTIONS, Ophthalmologic**).

ADVERSE REACTIONS (see full listing in **Supplemental Product Information**): **Adverse Drug Reaction Overview:** The safety of ZYVOXAM Tablets and Injection was evaluated in 2046 adult patients enrolled in seven phase III comparator-controlled clinical trials, who were treated for ≤28 days. In these studies, 85% of the adverse events reported with ZYVOXAM were described as mild to moderate in intensity. The most common adverse events in patients treated with ZYVOXAM were diarrhea (incidence across studies: 2.8-11.0%), headache (incidence across studies: 0.5-11.3%) and nausea (incidence across studies: 3.4-9.6%). Other adverse events reported in phase II and phase III studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus and tongue discolouration.

Postmarket Adverse Drug Reactions: Myelosuppression (anemia including pure red blood cell aplasia, leukopenia, pancytopenia and thrombocytopenia) has been reported during post-marketing use of ZYVOXAM (see **WARNINGS AND PRECAUTIONS**). Peripheral neuropathy and 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 **WARNINGS AND PRECAUTIONS**). Lactic acidosis (see **WARNINGS AND PRECAUTIONS, General**), convulsions (see **WARNINGS AND PRECAUTIONS, Neurologic**), angioedema and anaphylaxis have been reported. Very rare reports of bullous skin disorders such as those described as Stevens-Johnson syndrome have been received. Very rare spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic agents have been reported (see **WARNINGS AND PRECAUTIONS, Drug Interactions**).

These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOXAM or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established.

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug, you may notify Health Canada by toll-free telephone: 1-866-234-2345.

DRUG INTERACTIONS (also see **Supplemental Product Information**): **Overview: Drugs Metabolized by Cytochrome P450:** Linezolid is not an inducer of cytochrome P450 (CYP) in rats. It is not detectably metabolized by human cytochrome P450 and it does not 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. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Drug-Drug Interactions: Monoamine Oxidase Inhibition: Linezolid is a mild reversible nonselective inhibitor of MAO-A and MAO-B. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents. Studies in healthy volunteers have examined the effect of linezolid on the pharmacodynamic responses to tyramine, sympathomimetic amines and dextromethorphan (see **CONTRAINDICATIONS**).

Adrenergic Agents: A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of >100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content. A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects. Some individuals receiving ZYVOXAM may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response. A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone and the combination of steady-state linezolid (600 mg q12h for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments. Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2 to 3 hours after the second dose of PPA or PSE, and returned to baseline 2 to 3 hours after peak.

Serotonergic Agents: A study to assess the potential interaction of linezolid with a serotonin-reuptake inhibitor (dextromethorphan) was conducted in healthy volunteers. No significant differences were found in the pharmacodynamic measures of temperature, digit symbol substitution, nurse-rated sedation, blood pressure or pulse when subjects were administered dextromethorphan with or without linezolid. The effects of other serotonin-reuptake inhibitors have not been studied. Very rare spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic agents have been reported. 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 (see **CONTRAINDICATIONS**).

Antibiotics: Aztreonam – The pharmacokinetics of linezolid or aztreonam are not altered when administered together. Gentamicin – The pharmacokinetics of linezolid or gentamicin are not altered when administered together.

Antacids: No studies have been conducted with antacids and chelating agents. Based on the chemical structure, concurrent administration with these agents is not expected to affect absorption of linezolid.

Drug-Food Interactions: Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOXAM. Quantities of tyramine consumed should be <100 mg/meal. Foods high in tyramine content include

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those that may have undergone protein changes by aging, fermentation, pickling or smoking to improve flavour, such as aged cheeses (0-15 mg tyramine/28 g); fermented or air-dried meats (0.1-8 mg tyramine/28 g); sauerkraut (8 mg tyramine/224 g); soy sauce (5 mg tyramine/1 tsp); tap beers (4 mg tyramine/360 mL); red wines (0-6 mg tyramine/240 mL). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

Administration

DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment:
The recommended dosage for ZYVOXAM Tablets, Injection and Oral Suspension for the treatment of infections in adults is described in Table 1. Doses of ZYVOXAM are administered every 12 hours (q12h).

Table 1. Dosage Guidelines for ZYVOXAM

Infection*	Dosage and Route of Administration	Recommended Duration of Treatment (consecutive days)
Vancomycin-resistant *Enterococcus faecium* (VREF) infections, including concurrent bacteremia	600 mg IV or oral q12h	14 to 28
Nosocomial pneumonia	600 mg IV or oral q12h	10 to 14
Complicated skin and skin structure infections: a) Except diabetic foot infections b) Non-limb threatening diabetic foot infections, without concomitant osteomyelitis	600 mg IV or oral q12h 600 mg IV or oral q12h	10 to 14 14 to 28
Community-acquired pneumonia, including concurrent bacteremia	600 mg IV or oral q12h	10 to 14
Uncomplicated skin and skin-structure infections	400 mg oral q12h	10 to 14

* Due to the designated pathogens (see **INDICATIONS AND CLINICAL USE**)

Patients with infection due to MRSA should be treated with ZYVOXAM 600 mg q12h.

In controlled clinical trials, the protocol-defined duration of treatment for all infections ranged from 7 to 28 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response.

No dose adjustment is necessary when switching from intravenous (IV) to oral administration. Patients whose therapy is started with ZYVOXAM Injection may be switched to ZYVOXAM Tablets or Oral Suspension at the discretion of the physician, when clinically indicated. ZYVOXAM may be taken with or without food.

Missed Dose: If a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule resumed. Doses should not be doubled.

Administration: Intravenous (IV): ZYVOXAM Injection should be administered by IV infusion over a period of 30-120 minutes. **Do not use this IV infusion bag in series connections.** Additives should not be introduced into this solution. If ZYVOXAM Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product. If the same IV line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of ZYVOXAM Injection with an infusion solution compatible with ZYVOXAM Injection and with any other drug(s) administered via this common line (see **DOSAGE AND ADMINISTRATION, Compatible IV Solutions**).

ZYVOXAM Injection: ZYVOXAM Injection is supplied as a ready-to-use sterile isotonic solution for IV infusion. As with all parenteral drug products, IV solutions should be inspected visually for clarity, particulate matter, precipitate and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate or leakage should not be used. ZYVOXAM Injection may exhibit a yellow colour that can intensify over time without adversely affecting potency. Discard unused portions.

Compatible IV Solutions: 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP.

Compatibility: Physical incompatibilities resulted when ZYVOXAM Injection was combined with the following drugs during simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium and trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when ZYVOXAM Injection was combined with ceftriaxone sodium.

Supplemental Product Information

Information for Patients

Patients should inform their physician or pharmacist if they:

- Have a history of high blood pressure.
- Are taking any cold or flu remedies or decongestants containing pseudoephedrine.
- Are taking any antidepressants especially those known as serotonin re-uptake inhibitors.
- Are taking any other medicines, including those you have bought without a prescription.
- Have a history of anemia (low hemoglobin), thrombocytopenia (low platelets), neutropenia (low white blood cells) or any other blood-related disorders.
- Have a history of bleeding problems.
- Ever had any unusual or allergic reaction to ZYVOXAM or its ingredients (such as preservatives or dyes).
- Are pregnant or trying to become pregnant.
- Are breastfeeding.
- Have a history of seizures or convulsions.

ADVERSE REACTIONS: Clinical Trial Adverse Drug Reactions: *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Phase III Clinical Trials: Table 2 shows the incidence of drug-related adverse events reported in at least 1% of adult patients in these trials by dose of ZYVOXAM.

Table 2. Incidence of Drug-Related Adverse Events Occurring in >1% of Adult Patients Treated with ZYVOXAM in Comparator-Controlled Clinical Trials

	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
Adverse Event	ZYVOXAM 400 mg PO q12h (n=548)	Comparator (n=537)	ZYVOXAM 600 mg q12h (n=1498)	All Other Comparators (n=1464)
% of patients with at least 1 drug-related adverse event	25.4	19.6	20.4	14.3
% of patients discontinuing due to drug-related adverse events†	3.5	2.4	2.1	1.7
Diarrhea	5.3	4.8	4	2.7
Nausea	3.5	3.5	3.3	1.8
Headache	2.7	2.2	1.9	1
Taste alteration	1.8	2	0.9	0.2
Vaginal moniliasis	1.6	1.3	1	0.4
Fungal infection	1.5	0.2	0.1	<0.1
Abnormal liver function tests	0.4	0	1.3	0.5
Vomiting	0.9	0.4	1.2	0.4
Tongue discolouration	1.1	0	0.2	0
Dizziness	1.1	1.5	0.4	0.3
Oral moniliasis	0.4	0	1.1	0.4

† The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOXAM were nausea, headache, diarrhea and vomiting.

In controlled clinical trials, abdominal pain/cramp/distension and abnormal hematology tests were also reported occurring at an incidence of at least 1%.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse drug reactions that were possibly or probably related to ZYVOXAM with an incidence less than 1.0% but greater than 0.1% in controlled clinical trials were:

Body System	
Metabolic and nutritional	Amylase Increased, Hyperglycemia, Hyponatremia, Lipase High, Serum Creatine Phosphokinase Increased, AST Increased and ALT Increased
Special senses	Blurred Vision, Tinnitus
Musculo-skeletal	None
Hemic and lymphatic	Eosinophilia, Neutropenia, Thrombocytopenia
Respiratory	None
Cardiovascular	Hypertension, Phlebitis
Digestive	Constipation, Dry Mouth, Dyspepsia, Gastritis, Glossitis, Increased Thirst, Stomatitis and Tongue Discolouration
Nervous	Dizziness, Hypesthesia, Insomnia, Paresthesia
Body as a whole	Abdominal Pain, Chills, Diaphoresis, Fatigue, Fungal Infection, Injection/Vascular Catheter Site Pain and Injection/Vascular Catheter Site Phlebitis/Thrombophlebitis
Urogenital	Polyuria and Vaginitis/Vaginal Infection
Skin	Dermatitis, Moniliasis Skin, Pruritus, Rash and Urticaria

In controlled clinical trials the pattern of drug-related adverse reactions by body system with an incidence less than 1.0% but greater than 0.1% were similar to comparators.

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Serious adverse reactions in controlled clinical trials considered possibly or probably related to ZYVOXAM treatment with an incidence less than 0.1% were Hypertension, Kidney Failure, Liver Function Test Abnormality, Pancreatitis, Thrombocytopenia, Transient Ischemic Attacks and Vomiting.

Phase IV Clinical Trials: In a phase IV comparator-controlled study (Study 113) of adult diabetic patients with clinically documented complicated skin and skin structure infections ("diabetic foot infections"), most drug-related adverse events were rated as mild or moderate in intensity; 13.0% were rated as severe, and with the exception of diarrhea (0.8%), each severe drug-related event was reported in no more than one patient.

Table 3. Frequencies of Study-Emergent Drug-Related Adverse Events Reported for ≥1% of Patients in Either Treatment Group (Study 113, linezolid in the treatment of adult diabetic patients with clinically documented complicated skin and skin structure infections ["diabetic foot infections"])

		Treatment Group	
COSTART Body System Classification	**Adverse Event (Medically-Equivalent Term*)**	**Linezolid (n=241) n (%)†**	**Comparator (n=120) n (%)†**
Total reported	Patients reporting at least 1 drug-related AE	64 (26.6)	12 (10.0)
Digestive	Diarrhea	18 (7.5)	4 (3.3)
	Nausea	14 (5.8)	0
	Vomiting	4 (1.7)	1 (0.8)
	Dyspepsia	3 (1.2)	1 (0.8)
	Appetite decreased	3 (1.2)	0
Hemic and lymphatic	Anemia	11 (4.6)	0
	Thrombocytopenia	9 (3.7)	0

* The information represents the number (%) of patients who reported a given study-emergent adverse event. Any patient with multiple reports of the same event was counted only once for that event.
† All percentages are based on the number of ITT patients.

Less Common Clinical Trial Adverse Drug Reactions (<1%): In Study 113, adverse drug reactions that were possibly or probably related to ZYVOXAM with an incidence less than 1.0% but greater than 0.1% were:

Body System

Metabolic and nutritional	Healing Abnormal, Hypoglycemia, Hypokalemia, LDH Increased
Special senses	Taste Perversion
Musculo-skeletal	None
Hemic and lymphatic	Ecchymosis/Bruise, Neutropenia
Respiratory	Dyspnea
Cardiovascular	Congestive Heart Failure, Disorder Peripheral Vascular
Digestive	Anorexia, Biliary Pain, *C. difficile* Colitis, Cholestatic Jaundice, Disorder Gastrointestinal NOS, Disorder Rectal, Flatulence, Gastrointestinal Bleeding, Monilia Oral
Nervous	Disorientation, Dizziness, Somnolence
Body as a whole	Abdominal Cramp, Abdominal Pain Localized, Asthenia, Disorder Mucous Membrane, Fatigue, Headache, Fungal Infection NOS, Infection NEC, Laboratory Test Abnormality Other
Urogenital	None
Skin	Dermatitis, Dermatitis Fungal, Erythema, Rash, Ulcer Skin

Abbreviations: NEC=not elsewhere classified; NOS=not otherwise specified

In Study 113, serious drug-related events were reported for seven patients in the linezolid treatment group: congestive heart failure, peripheral vascular disease; biliary pain and cholestatic jaundice; *Clostridium difficile* colitis; gastrointestinal bleeding; anemia; and hypokalemia.

Phase III Clinical Trials: Abnormal Hematologic and Clinical Chemistry Findings: ZYVOXAM has been associated with thrombocytopenia when used in adults in doses up to and including 600 mg every 12 hours for up to 28 days. In phase III comparator-controlled trials, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOXAM and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. Thrombocytopenia associated with the use of ZYVOXAM appears to be dependent on duration of therapy (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in phase III clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOXAM; the role of linezolid in these events cannot be determined (see **WARNINGS AND PRECAUTIONS**). Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOXAM and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy and were reversible. The incidence of patients with at least one substantially abnormal hematologic or serum chemistry value is presented in Tables 4 and 5.

Table 4. Percent of Adult Patients who Experienced at Least One Substantially-Abnormal* Hematology Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOXAM

Laboratory Assay	**Uncomplicated Skin and Skin-Structure Infections**		**All Other Indications**	
	ZYVOXAM 400 mg q12h	**Comparator**	**ZYVOXAM 600 mg q12h**	**All Other Comparators**
Hemoglobin (g/L)	0.9	0.0	7.1	6.6
Platelet count (x 10^9/L)	0.7	0.8	3.0	1.8
WBC (x 10^9/L)	0.2	0.6	2.2	1.3
Neutrophils (x 10^9/L)	0.0	0.2	1.1	1.2

* <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline;
<75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

Table 5. Percent of Adult Patients who Experienced at Least One Substantially-Abnormal* Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials with ZYVOXAM

Laboratory Assay	**Uncomplicated Skin and Skin-Structure Infections**		**All Other Indications**	
	ZYVOXAM 400 mg q12h	**Comparator**	**ZYVOXAM 600 mg q12h**	**All Other Comparators**
AST (U/L)	1.7	1.3	5.0	6.8
ALT (U/L)	1.7	1.7	9.6	9.3
LDH (U/L)	0.2	0.2	1.8	1.5
Alkaline phosphatase (U/L)	0.2	0.2	3.5	3.1
Lipase (U/L)	2.8	2.6	4.3	4.2
Amylase (U/L)	0.2	0.2	2.4	2.0
Total bilirubin (µmol/L)	0.2	0.0	0.9	1.1
BUN (mmol/L)	0.2	0.0	2.1	1.5
Creatinine (µmol/L)	0.2	0.0	0.2	0.6

* >2 x Upper Limit of Normal (ULN) for values normal at baseline;
>2 x ULN and >2 x baseline for values abnormal at baseline.

Phase IV Clinical Trials: Table 6 shows the frequencies of selected abnormal hematologic test values in Study 113 at End of Treatment.

Table 6. Frequencies of Abnormal Values for Selected Hematology Assays at EOT (Study 113, linezolid in the treatment of adult diabetic patients with clinically-documented complicated skin and skin-structure infections ["diabetic foot infections"])

	Clinically-Significant Abnormal*/All abnormal values for assay	
Hematology Assay	**Linezolid n/N (%)**	**Comparator n/N (%)**
Hemoglobin	9/111 (8.1)	1/52 (1.9)
Hematocrit	6/112 (5.4)	1/49 (2.0)
WBC	2/26 (7.7)	1/12 (8.3)
Platelet count	9/43 (20.9)	3/16 (18.8)

Abbreviations: EOT=end of treatment, WBC=white blood count
* Abnormal values assessed by the investigator as clinically significant.

Table 7 summarizes abnormal chemistry values in Study 113 assessed at End of Treatment.

Table 7. Frequencies of Abnormal Values for Selected Chemistry Assays at EOT* (Study 113, linezolid in the treatment of adult diabetic patients with clinically-documented complicated skin and skin structure infections ["diabetic foot infections"])

	Clinically-Significant Abnormal*/All abnormal values for assay	
Chemistry Assay	**Linezolid n/N (%)**	**Comparator n/N (%)**
ALT	3/32 (9.4)	1/15 (6.7)
AST	1/24 (4.2)	1/19 (5.3)
Bicarbonate	1/22 (4.5)	0/15
Lactic dehydrogenase	3/38 (7.9)	0/16
Amylase	3/17 (17.6)	0/18

Abbreviations: ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, EOT=end of treatment
* Assessed by the investigator as clinically significant.

DRUG INTERACTIONS: Drug-Herb Interactions: Interactions with herbal products have not been established.

Drug-Laboratory Interactions: There are no reported drug-laboratory test interactions.

OVERDOSAGE: In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a phase I clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of ZYVOXAM was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

Product Monograph available on request.

References: 1. ZYVOXAM (linezolid) Product Monograph, Pfizer Canada Inc., October 2009. **2.** Ontario Drug Benefit Formulary/Comparative Drug Index. Accessed March 14, 2011.

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ZYVOXAM Tablets, Injection and Oral Suspension are indicated for the treatment of adult patients with the following infections, when caused by susceptible strains of the designated aerobic Gram-positive micro-organisms:

Complicated skin and skin structure infections, including non-limb-threatening diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes* or *Streptococcus agalactiae*. ZYVOXAM has not been studied in the treatment of necrotizing fasciitis or decubitus ulcers.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

ZYVOXAM is not indicated for treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

ZYVOXAM Tablets, Injection and Oral Suspension should not be used in patients taking or within 2 weeks of taking any medicinal product which inhibits monoamine oxidases A or B. Unless patients are monitored for potential increases in blood pressure, ZYVOXAM should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis or patients taking directly or indirectly acting sympathomimetic agents, vasopressive agents or dopaminergic agents. Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOXAM should not be administered to patients with carcinoid syndrome or patients taking serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine or buspirone.

The most common clinical trial adverse events in patients treated with ZYVOXAM were (incidence across studies): diarrhea (2.8% to 11.0%); headache (0.5% to 11.3%); and nausea (3.4% to 9.6%).

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

Myelosuppression 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 at least weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, patients who are at increased risk for bleeding, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or decreased hemoglobin levels or platelet counts or function, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with ZYVOXAM should be considered in patients who develop or have worsening myelosuppression.

Visual function should be monitored in all patients taking ZYVOXAM for longer than the maximum recommended duration and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOXAM.

Please see Product Monograph for complete Warnings and Precautions, Dosage and Administration. Product Monograph available on request.

cSSSI=complicated skin and skin structure infection; MRSA=methicillin-resistant *Staphylococcus aureus*
* Clinical significance is unknown.

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See prescribing summary on page A17

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