

久裕企業股份有限公司 函

公司地址：新北市中和區中正路 880 號 14 樓之 5

聯絡電話：02-82277999 分機 2201

聯絡人：顏嘉琪

受文者：醫院/診所/藥局

發文日期：中華民國 110 年 04 月 26 日

發文字號：字第 11004021 號

速別：普通件

密等及解密條件或保密期限：

附件：新包裝照片/仿單變更處/新版仿單/衛生福利部核准公文

ZYVI

主旨：本公司經銷藥品 Zyvox Tablets 600mg(采福適膜衣錠 600 毫克，衛署藥輸字第 023181 號)-包裝及仿單變更通知

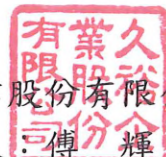
說明：

- 一、本公司為輝瑞大藥廠股份有限公司之經銷商。
- 二、輝瑞大藥廠藥品 Zyvox Tablets 600mg(采福適膜衣錠 600 毫克，衛署藥輸字第 023181 號)，自批號 EF6300 起包裝上藥商地址變更為台北市信義區松仁路 100 號 42-43 樓。
- 三、仿單內容更新，變更內容詳見附件標示處(新仿單版本為 USPI 201807-2)
- 四、此次變更係依衛生福利部核准發文字號:衛授食字第 1096015532 號，是項藥品之成分、健保代碼及健保售價均無改變，敬請惠予繼續使用，不勝感激！

順頌 商祺

正本：醫院/診所/藥局

副本：

久裕企業股份有限公司
負責人：傅輝東

~新包裝照片~





采福適服衣錠

ZYVOX Tablets 600mg

衛署簡輸字第023181號

本藥須由醫師處方使用

為了減少形成抗藥性細菌，維持 ZYVOX 製劑及其他抗菌劑的有效性，ZYVOX 僅應用於治療或預防被證實或強烈懷疑由細菌引起的感染。

ZYVOX 製劑使用超過 28 天的安全性和有效性，尚未在有對照組的臨床試驗中評估過。

1. 適應症

治療由下列感受性菌株感染的病人

Vancomycin 抗藥性的 *Enterococcus faecium* 感染，包括併發菌血症的病例。

醫院感染的肺炎，由 *Staphylococcus aureus*(對 methicillin 有感受性和對 methicillin 有抗藥性的菌株)或 *Streptococcus pneumoniae*(對 penicillin 有感受性的菌株)所引起。

複雜性皮膚和皮膚構造感染，包括蜂窩織炎感染，無併發骨髓炎，由 *Staphylococcus aureus*(對 methicillin 有感受性和對 methicillin 有抗藥性的菌株)、*Streptococcus pyogenes* 或 *Streptococcus agalactiae* 所引起。

非複雜性皮膚和皮膚構造感染，由 *Staphylococcus aureus*(僅限於對 methicillin 有感受性的菌株)或 *Streptococcus pyogenes* 所引起。

社區感染的肺炎，由 *Streptococcus pneumoniae*(僅限於對 penicillin 有感受性的菌株)，包括併發菌血症的病例，或 *Staphylococcus aureus*(僅限於對 methicillin 有感受性的菌株)所引起。

說明：為減少抗藥性菌種的形成，維持 ZYVOX 及其他抗菌藥物的有效性，ZYVOX 僅可用於治療或預防被證實或強烈懷疑是由感受性細菌所引起的感染，得到培養及感受性試驗的結果後，應根據結果選擇或調整抗菌治療。若無此種資料，則可根據當地的流行病學及感受性型態的經驗開始治療。本藥不適用於格蘭氏陰性菌感染的治療。若確定或懷疑同時感染格蘭氏陰性菌，立即開始特定的格蘭氏陰性菌治療是非常重要的(參閱警語及注意事項)。

2. 用法用量

表一列為治療感染時，ZYVOX 製劑的建議使用劑量。

表一：ZYVOX 的劑量使用標準

感 染*	劑量、使用途徑和頻率		建議治療期(連續的天數)
	兒童病人 ¹ (從出生至 11 歲)	成人及青少年(12 歲以上)	
複雜性皮膚和皮膚組織的感染	10mg/kg 靜脈注射或口服 ² 每 8 小時一次	600mg 靜脈注射或口服 ² 每 12 小時一次	10 至 14
社區感染的肺炎，包括併發菌血症的病例			
院內感染的肺炎			
Vancomycin 抗藥性 <i>Enterococcus faecium</i> 感染，包括併發菌血症的病例	10mg/kg 靜脈注射或口服 ² 每 8 小時一次	600mg 靜脈注射或口服 ² 每 12 小時一次	14 至 28
非複雜性皮膚和皮膚組織的感染	未滿 5 歲：10mg/kg 口服 ² ， 每 8 小時一次 5-11 歲：10mg/kg 口服 ² ， 每 12 小時一次	成人：400mg 口服 ² ，每 12 小時一次 青少年：600mg 口服 ² ， 每 12 小時一次	10 至 14

* 由特定之病原菌所引起(參閱適應症(1))

¹ 新生兒出生未滿 7 天：大多數出生未滿 7 天的早產兒(孕齡未滿 34 週)比許多足月產新生兒和年紀較大的嬰兒具有更低的 linezolid 血清濃度和更大的 AUC 值，因此這些新生兒的起始劑量應該是 10mg/kg q12h。對於臨床治療反應不佳的新生兒，可考慮給與 10 mg/kg q8h 的劑量，所有的新生兒病人都該接受 10 mg/kg q8h 治療 7 天(參閱臨床藥理學(12.3))；特定族群使用—兒童使用 (8.4)。

² 口服時，可用 ZYVOX 錠劑或口服懸浮劑。

因 methicillin-resistant *Staphylococcus aureus* (MRSA)感染的成人病人應使用 ZYVOX 600mg，每 12 小時一次予以治療。

在對照臨床試驗中，對於各種感染，試驗計劃書中所定義的治療期間為 7 至 28 天。治療時間的長短應由主治醫師根據感染的部位和嚴重程度及病人的臨床反應來決定。

當病人由靜脈注射改為口服時，並不需要調整劑量。當臨床上需要時，可由醫師決定將靜脈注射改為 ZYVOX 錠劑或口服懸浮劑。

1

2

3. 劑型與劑量

錠 劑

600mg (白色、膠囊形狀之膜衣錠，表面印有“ZYVOX 600mg”)

4. 禁忌

4.1 過敏

對 linezolid 或產品中其他成分過敏者禁用 ZYVOX。

4.2 單胺氧化酶抑制劑

Linezolid 不可用於正在使用任何會抑制單胺氧化酶 A 或 B 之藥物(如 phenelzine、isocarboxazid)或已停用任何此類藥物但未超過兩週的病人。

5. 警語及注意事項

5.1 骨髓抑制接受 linezolid 的病人曾有發生骨髓抑制(包括貧血、白血球減少、全系列白血球減少和血小板減少)的報告，就已如案例而言，當停用 linezolid 後，受影響的血球參數會回升到治療前的數值。接受 linezolid 的病人應每週監測全血球計數，特別是接受 linezolid 治療超過兩週者、已有骨髓抑制狀況者、同時併用會造成骨髓抑制之藥物者、或先前已接受或同時接受抗生素治療的慢性感染病人。對於發生骨髓抑制或骨髓抑制狀態惡化的病人，應考慮停止 linezolid 治療。

5.2 週邊神經病變及視神經病變

ZYVOX 治療之病人曾有週邊神經及視神經病變被報導過，這些病人接受治療的療程都比最大建議療程 28 天更久。病人接受長期治療超出最大建議療程，若發生視神經病變者，會逐漸失去視力，部份接受 ZYVOX 少於 28 天治療之病人，曾有視力模糊的報告。兒童病人也有週邊神經病變與視神經病變的報告。

若病人有視力受損的症狀出現者，如視力改變、視覺色彩改變、視力模糊或視野缺損等，建議應立即作視力評估。若病人長期使用(≥3 個月)ZYVOX，應監測其視力功能且不論接受 ZYVOX 治療期長短，所有病人都應回報最近的視力症狀。若有週邊或視神經病變發生，ZYVOX 慎用與否應權衡其可能的危險性。

5.3 血清素症候群

併用 ZYVOX 及血清素類製劑，包括抗憂鬱劑(如選擇性血清素回收抑制劑)曾有相關的血清素症狀的自發性報告，包括死亡病例。

除非臨床情況適合，且能仔細監測病人的血清素徵象或症狀，或者類抗精神藥物急性性(類 NMS)反應，否則 linezolid 不應該授予類癱瘓症狀，或服用下列藥物的病人：血清素再吸收抑制劑、三環抗憂鬱劑、血清素 5-HT₁ 受體促進劑 (triptans)、meperidine、bupropion、buspirone(參閱藥物交互作用(7)和臨床藥理學 (12.3))。

當在臨床上適合併用 ZYVOX 及血清素類製劑時，應密切觀察病人有無血清素症候群的徵候與症狀，例如認知功能障礙、過高熱、反射過度、協調不能。有些病例服用血清素抑制劑或 buspirone 的病人可能需要 linezolid 緊急治療。如果無法取得 linezolid 的替代藥物，且使用 linezolid 的可能益大於血清素症狀或類 NMS 反應的風險，則應立即停用血清素抑制劑，並授予 linezolid。須監測病人 2 週(服用 fluoxetine 的病人需 5 週)，或直到授予最後一劑 linezolid 後 24 小時為止，以先發生者為準。血清素症候群或類 NMS 反應的症狀，包括高熱、僵直、肌陣攣、自律神經失調、精神狀態變化(包括極度躁動、(惡化為譫妄和昏迷))。也應監測病人抗憂鬱劑的停藥症狀(關於停藥症狀的描述，請見特定藥物之仿單)。

5.4 針對導管相關之血流感染病人(含導管裝置部位感染)之一項研究性試驗所出現的死亡失平衡現象(Mortality Imbalance)

一項針對血管內導管相關感染之重症病人的開放性試驗中發現，接受 linezolid 治療者相對於接受 vancomycin/dicloxacillin/oxacillin 治療者有死亡率失平衡的現象[78/363 (21.5%) 比 58/363 (16.0%)]；勝率 1.426，95%信賴區間 0.970，2.098]，雖然因果關係尚未建立，這種失平衡現象主要發生於接受 linezolid 治療之病人其基準值測得格蘭氏陰性病原菌或混合格蘭氏陰性及陽性病原菌或未測得任何病原菌者，但在僅有格蘭氏陽性菌感染的病人中並未觀察到此死亡率失平衡現象。

Linezolid 尚未核准也不應用於治療導管相關血流感染或導管裝置部位感染之病人。

Linezolid 對於格蘭氏陰性病原菌並無臨床活性，故不能用於治療格蘭氏陰性菌感染。若確定或懷疑同時感染格蘭氏陰性菌，立即開始特定的格蘭氏陰性菌治療是非常重要的(參閱適應症(1))。

5.5 Clostridium difficile 相關之腹瀉

幾乎所有的抗菌劑，包括 ZYVOX，均有報告會引起 *Clostridium difficile* 相關之腹瀉(CDAD)，其症狀可由輕度腹瀉。使用抗菌劑治療會改變結腸內的正常菌叢而導致 *Clostridium difficile* 的過度生長。

Clostridium difficile 所產生的毒素 A 和 B 會造成 CDAD，產生超毒素(hypertoxin)的 *Clostridium difficile* 菌株會導致升高致病率及死亡率，因為這些感染能對抗微生物

3

4

劑的治療且可能需要進行結腸切除手術。所有使用抗生素後出現腹瀉的病人都應考慮發生 CDAD 的可能性。

由於曾有報告顯示 CDAD 會在使用抗菌劑超過兩個月以外才發生，仔細評估病人的疾病史是必要的。

一旦懷疑或確定是 CDAD，正在使用中的抗生素若非針對 *Clostridium difficile*，則可能需要停止，若有臨床上的需要，應給予適度的液體及電解質處置、蛋白質補充、針對 *Clostridium difficile* 的抗生素治療和手術的評估。

5.6 可能發生會導致血壓升高的交互作用

除非能夠針對病人監視可能出現的血壓升高現象，否則 linezolid 不可用於患有未獲控制之高血壓、嗜路細胞瘤、甲狀腺毒症的病人，以及(或)正在使用下列各類藥物的病人：直接與間接作用性擬交感神經作用劑(如 pseudoephedrine)、血管升壓劑(如 epinephrine、norepinephrine)、多巴胺類藥物(如 dopamine、dobutamine)(參閱藥物交互作用(7)和臨床藥理學(12.3))。

5.7 乳酸酸中毒

使用 ZYVOX 曾有引起乳酸性酸中毒的報告，所報導的案例，病人發生多次噁心嘔吐。當病人發生復發性噁心嘔吐、無法解釋的酸中毒、或接受 ZYVOX 期間重碳酸鹽濃度低時，應該立即接受醫療評估。

5.8 癰癤

曾有病人接受 linezolid 治療時發生癰癤的報告。在其中一些報告病例中，病人有癰癤病史和癰癤危險因子之情形。

5.9 低血糖

在上市後的使用經驗中，曾有正在接受胰島素或口服降血糖藥物治療的糖尿病病人於使用 linezolid (一種可逆性、不具選擇性的 MAO 抑制劑)治療時發生症狀性低血糖的病例報告。有些 MAO 抑制劑也曾使正在接受胰島素或口服降血糖藥物治療的糖尿病病人發生低血糖事件。雖然 linezolid 與低血糖之間的因果關係尚未確立，仍應提醒糖尿病病人，在使用 linezolid 治療時可能會發生低血糖反應。如果發生低血糖反應，可能必須降低胰島素或口服降血糖藥物的劑量，或是停用口服降血糖藥物、胰島素或 linezolid。

5.10 引發抗藥性細菌

在沒有被證實或強烈懷疑的細菌感染之狀況下或基於預防性目的，便使用 ZYVOX，對病人並無裨益，也會增加出現抗藥性細菌的危險。

6. 不良反應

6.1. 臨床試驗經驗

由於各項臨床試驗的條件差異很大，因此一藥物的臨床試驗不良反應率無法直接與另一藥物的臨床試驗不良反應率比較，也未必能反映臨床實務的情況。

成人病人

ZYVOX 製劑的安全性已在 2046 名接受 ZYVOX 治療期間達 28 天的 7 個第三期對照臨床試驗中接受評估。

在非複雜性皮膚和皮膚組織感染 (uSSSIs) 治療的病人中，25.4% 接受 ZYVOX 治療的病人與 19.6% 的對照組病人至少經歷一次藥物相關不良反應。在其他適應症方面，20.4% 接受 ZYVOX 治療的病人與 14.3% 的對照組病人至少經歷一次藥物相關不良反應。

表二所示為這些臨床試驗中，於成人發生率至少大於 1%，所有因果關係的、治療後出現的不良反應發生率。

表二：對照臨床試驗中，接受 ZYVOX 治療的成人病人中，其發生率大於 1% 之治療後出現的不良反應

不良反應	非複雜性皮膚和皮膚組織的感染		其他適應症 [†]	
	ZYVOX 400mg 每 12 小時一次、口服 (n=548)	Clarithromycin 250mg 每 12 小時一次、口服 (n=537)	ZYVOX 600mg 每 12 小時一次 (n=1498)	其他對照 品* (n=1464)
頭痛	8.8	8.4	5.7	4.4
腹瀉	8.2	6.1	8.3	6.4
噁心	5.1	4.5	6.6	4.6
嘔吐	2.0	1.5	4.3	2.3
暈眩	2.6	3.0	1.8	1.5
皮疹	1.1	1.1	2.3	2.6
貧血	0.4	0	2.1	1.4
味覺改變	1.8	2.0	1.0	0.3

陰道念珠菌病	1.8	1.3	1.1	0.5
口腔念珠菌病	0.5	0	1.7	1.0
肝功能檢測異常	0.4	0.2	1.6	0.8
細菌感染	1.5	0.2	0.3	0.2
舌頭變色	1.3	0	0.3	0
局部腹痛	1.3	0.6	1.2	0.8
泛發性腹痛	0.9	0.4	1.2	1.0
(Generalized abdominal pain)				

* 對照組包括 cefpodoxime proxetil 200mg 每 12 小時一次、口服；ceftriaxone 1g 每 12 小時一次、靜脈注射；dicloxacillin 500mg 每 6 小時一次、口服；oxacillin 2g 每 6 小時一次、靜脈注射；vancomycin 1g 每 12 小時一次、靜脈注射。

治療 uSSSIs 的病人中，接受 ZYVOX 治療的病人與對照組病人中分別有 3.5% 和 2.4% 由於藥物相關不良反應而停止治療。在其他適應症方面，接受 ZYVOX 治療的病人與對照組病人中分別有 2.1% 和 1.7% 由於藥物相關不良反應而停止治療。導致停止治療的最常見藥物相關不良反應為噁心、頭痛、腹瀉、嘔吐。

兒童病人

已在 215 名年紀從出生到 11 歲的兒童病人，以及 248 名 5 歲至 17 歲的兒童病人(這 248 人中，5 歲至 11 歲 146 人，12 歲至 17 歲 102 人)中評估 ZYVOX 製劑的安全性。這些病人被選入二個第三期對照臨床試驗中，接受 ZYVOX 治療 28 天。在遭受革蘭氏陽性菌感染的住院兒童病人(出生到 11 歲)研究中，病人以二比一的比例隨機接受 linezolid 或 vancomycin 治療，死亡率為 linezolid 治療組 6.0%(13/215)，vancomycin 治療組 3.0%(3/101)。然而，因為這個病人群有嚴重的原有疾病，所以無法確立死亡結果與藥物治療之因果關係。

治療 uSSSIs 的兒童病人中，接受 ZYVOX 治療的病人與對照組病人中分別有 19.2% 和 14.1% 至少經歷一次藥物相關不良反應。在其他適應症方面，接受 ZYVOX 治療的病人與對照組病人中分別有 18.8% 和 34.3% 至少經歷一次藥物相關不良反應。

表三所示為第三期對照臨床試驗中，在接受任一治療的兒童病人，其發生率大於 1%(且超過一名病人)，所有因果關係之治療後出現的不良反應。

表三：對照臨床試驗中，在接受任一治療的兒童病人，其發生率大於 1% 之治療後出現的不良反應

不良反應	複雜性皮膚和皮膚組織的感染*		其他適應症 [†]	
	ZYVOX (n=248)	Cefadroxil (n=251)	ZYVOX (n=215)	Vancomycin (n=101)
腹瀉	7.8	8.0	10.8	12.1
嘔吐	2.9	6.4	9.4	9.1
頭痛	6.5	4.0	0.9	0
貧血	0	0	5.6	7.1
血小板減少症	0	0	4.7	2.0
噁心	3.7	3.2	1.9	0
泛發性腹痛	2.4	2.8	0.9	2.0
局部腹痛	2.4	2.8	0.5	1.0
稀便	1.6	0.8	2.3	3.0
嗜紅紅血球增多	0.4	0.8	1.9	1.0
非給藥部位瘙癢	0.8	0.4	1.4	2.0
眩暈	1.2	0.4	0	0

* 5-11 歲病人接受 ZYVOX 10mg/kg 每 12 小時一次、口服，或 cefadroxil 15mg/kg 每 12 小時一次、口服；12 歲以上病人接受 ZYVOX 600mg 每 12 小時一次、口服，或 cefadroxil 500mg 每 12 小時一次、口服。

[†] 年紀從出生到 11 歲的病人接受 ZYVOX 10mg/kg 每 8 小時一次、靜脈注射，或根據年齡及腎臟清除率接受 vancomycin 10-15mg/kg 每 6-24 小時一次、靜脈注射。

治療 uSSSIs 的兒童病人中，接受 ZYVOX 治療的病人與對照組病人中分別有 1.6% 和 2.4% 至少經歷一次藥物相關不良反應。在其他適應症方面，接受 ZYVOX 治療的病人與對照組病人中分別有 0.9% 和 6.1% 由於藥物相關不良反應而停止治療。

實驗室檢測值異常

當使用劑量到達每 12 小時一次 600 毫克，治療期長達 28 天時，ZYVOX 會造成血小板減少症。在第三期對照臨床試驗中，ZYVOX 組發生顯著血小板數目減少(定義為比正常下限值和/或基準之 75% 還低者)的病人百分比在為 2.4%(各試驗中的發生率範圍：0.3% 至 10.0%)，而對照組為 1.5%(各試驗中的發生率範圍：0.4% 至 7.0%)。在一個以出生至 11 歲的住院兒童病人為對象的研究中，ZYVOX 組發生顯著血小板數目減少(定義為比正常下限值和/或基準之 75% 還低者)的病人百分比在為 12.9%，而 vancomycin 組為 13.4%。在一個以 5-17 歲的門診兒童病人為對象的研究中，ZYVOX

組發生顯著血小板數目減少的病人百分比在為 0%，而 cefadroxil 組為 0.4%。ZYVOX 所造成血小板減少症與治療期間的長短有關(一般是大於 2 週的治療)。在停止治療後，大部份病人的血小板數目會在追蹤期間回復到正常範圍和/或基線。在第三期對照臨床試驗中，發生血小板減少症的病人並未產生其他相關的不良反應。在 ZYVOX 的人道療法計劃中，發生血小板減少症的病人曾發生出血的事件；linezolid 在此事件所扮演的角色尚未被確立(參閱警語及注意事項(5.1))。

不管是否與藥品有關，其他實驗室檢測數值改變在 ZYVOX 組和對照組之間並沒有顯著的差異。這些實驗室檢測數值改變不具臨床重要性，不會導致需要停藥，而且是可逆的。表四、五、六、和表七所列為至少出現一次顯著異常的血液學或血清生化檢驗值之成年和兒童病人百分比。

表四：在 ZYVOX 對照臨床試驗中，至少出現一次顯著異常的*血液學檢驗值之成人病人百分比

實驗室檢測	非複雜性皮膚和皮膚組織的感染		其他適應症	
	ZYVOX 400mg 每12小時一次	Clarithromycin 250mg 每12小時一次	ZYVOX 600mg 每12小時一次	其他對照品 [†]
血紅素 Hemoglobin (g/dL)	0.9	0.0	7.1	6.6
血小板數目 Platelet count($\times 10^3/\text{mm}^3$)	0.7	0.8	3.0	1.8
白血球數目 WBC($\times 10^3/\text{mm}^3$)	0.2	0.6	2.2	1.3
嗜中性白血球數目 Neutrophils($\times 10^3/\text{mm}^3$)	0.0	0.2	1.1	1.2

* 基線數值正常時，比正常下限值之 75% 還低者(比較嗜中性白血球數目時，則取比 50% 還低者)；

基線數值不正常時，比正常下限值和基線數值之 75% 還低者(比較嗜中性白血球數目時，則取比 50% 還低者)；

[†] 對照組包括 cefpodoxime proxetil 200mg 每 12 小時一次、口服；ceftriaxone 1g 每 12 小時一次、靜脈注射；dicloxacillin 500mg 每 6 小時一次、口服；oxacillin 2g 每 6 小時一次、靜脈注射；vancomycin 1g 每 12 小時一次、靜脈注射。

表五：在 ZYVOX 對照臨床試驗中，至少出現一次顯著異常的*血清生化檢驗值之成人病人百分比

實驗室檢測	非複雜性皮膚和皮膚組織的感染		其他適應症	
	ZYVOX 400mg 每12小時一次	Clarithromycin 250mg 每12小時一次	ZYVOX 600mg 每12小時一次	其他對照品 [†]
AST(U/L)	1.7	1.3	5.0	6.8
ALT(U/L)	1.7	1.7	9.6	9.3
乳酸脫氫酶 (LDH)(U/L)	0.2	0.2	1.8	1.5
鹼性磷酸酶 (Alkaline phosphatase)(U/L)	0.2	0.2	3.5	3.1
脂酶 (Lipase)(U/L)	2.8	2.6	4.3	4.2
澱粉酶 (Amylase)(U/L)	0.2	0.2	2.4	2.0
總膽紅素 (Total bilirubin) (mg/dL)	0.2	0.0	0.9	1.1
尿素氮 (BUN)(mg/dL)	0.2	0.0	2.1	1.5
肌酸酐 (Creatinine)(mg/dL)	0.2	0.0	0.2	0.6

* 基線數值正常時，比正常上限值之 2 倍還高者；

基線數值不正常時，比正常上限值之 2 倍和基線數值之 2 倍還高者。

[†] 對照組包括 cefpodoxime proxetil 200mg 每 12 小時一次、口服；ceftriaxone 1g 每 12 小時一次、靜脈注射；dicloxacillin 500mg 每 6 小時一次、口服；oxacillin 2g 每 6 小時一次、靜脈注射；vancomycin 1g 每 12 小時一次、靜脈注射。

表六：在 ZYVOX 對照臨床試驗中，至少出現一次顯著異常的*血液學檢驗值之兒童病人百分比

實驗室檢測	非複雜性皮膚和皮膚組織感染 [†]		其他適應症 [‡]	
	ZYVOX	Cefadroxil	ZYVOX	Vancomycin
血紅素(Hemoglobin)(g/dL)	0.0	0.0	15.7	12.4

血小板數目(Platelet count)($\times 10^3/\text{mm}^3$)	0.0	0.4	12.9	13.4
白血球數目(WBC)($\times 10^3/\text{mm}^3$)	0.8	0.8	12.4	10.3
嗜中性白血球數目(Neutrophils)($\times 10^3/\text{mm}^3$)	1.2	0.8	5.9	4.3

* 基線數值正常時，比正常下限值之 75% 還低者(比較嗜中性白血球數目時，則取比 50% 還低者)；

基線數值不正常時，比正常下限值之 75% (比較嗜中性白血球數目時，則取比 50% 還低者)和基線數值之 75% 還低者 (如果基線數值低於正常下限值，比較嗜中性白血球數目時，則取比 50% 還低者；比較血紅素時，則取比 90% 還低者)；

[†] 5-11 歲病人接受 ZYVOX 10mg/kg 每 12 小時一次、口服，或 cefadroxil 15mg/kg 每 12 小時一次、口服，12 歲以上病人接受 ZYVOX 600mg 每 12 小時一次、口服，或 cefadroxil 500mg 每 12 小時一次、口服。

[‡] 年紀從出生到 11 歲的病人接受 ZYVOX 10mg/kg 每 8 小時一次、靜脈注射，或根據年齡及腎臟清除率接受 vancomycin 10-15mg/kg 每 6-24 小時一次、靜脈注射。

表七：在 ZYVOX 對照臨床試驗中，至少出現一次顯著異常的*血清生化檢驗值之兒童病人百分比

實驗室檢測	非複雜性皮膚和皮膚組織的感染 [†]		其他適應症 [‡]	
	ZYVOX	Cefadroxil	ZYVOX	Vancomycin
ALT(U/L)	0.0	0.0	10.1	12.5
脂酶 Lipase (U/L)	0.4	1.2	—	—
澱粉酶 Amylase(U/L)	—	—	0.6	1.3
總膽紅素 Total bilirubin (mg/dL)	—	—	6.3	5.2
肌酸酐 Creatinine(mg/dL)	0.4	0.0	2.4	1.0

* 基線數值正常時，比正常上限值之 2 倍還高者；

基線數值不正常時，比正常上限值之 2 倍和基線數值之 2 倍還高者(比較總膽紅素時，則取比 1.5 倍還高者)；

[†] 5-11 歲病人接受 ZYVOX 10mg/kg 每 12 小時一次、口服，或 cefadroxil 15mg/kg 每 12 小時一次、口服，12 歲以上病人接受 ZYVOX 600mg 每 12 小時一次、口服，或 cefadroxil 500mg 每 12 小時一次、口服。

[‡] 年紀從出生到 11 歲的病人接受 ZYVOX 10mg/kg 每 8 小時一次、靜脈注射/口服，或根據年齡及腎臟清除率接受 vancomycin 10-15mg/kg 每 6-24 小時一次、靜脈注射。

6.2. 上市後的經驗

以下是 ZYVOX 核准上市後出現的不良反應。因為主動通報者的族群大小不明，所以無法正確估算這些反應的發生頻率或確定它們與藥物暴露的因果關係：

- 骨髓抑制(包括貧血、白血球減少、全部血球減少、及血小板減少)(參閱警語及注意事項(5.1))；含鐵血球芽細胞貧血(sideroblastic anemia)。
- 周邊神經病變及視神經病變，有時會逐漸失去視力 (參閱警語及注意事項(5.2))。
- 乳酸性酸中毒 (參閱警語及注意事項(5.7))。雖然這些事件主要發生在治療期比最大建議治療期 28 天還久的病人，治療期較短的病人也有發生此類事件之報告。
- 病人併用血清素類藥物，包括抗憂鬱劑 (如選擇性血清素回收抑制劑) 及 ZYVOX 曾有相關的血清素症狀的報告(參閱警語及注意事項(5.3))。
- 癲癇 (參閱警語及注意事項(5.8))。
- 過敏反應、血管性水腫及大泡性皮膚異常包含嚴重型皮膚藥物過敏反應(例如毒性表皮溶解症及 Steven-Johnson 症候群之皮膚異常)。
- 曾有在使用 linezolid 時發生牙齒表面變色及舌頭變色的報告。在已知出現這種現象的病人中，經過專業的牙科清潔(人工洗牙)之後，牙齒變色的現象可以處理。
- 低血糖，包括症狀性低血糖(參閱警語及注意事項(5.9))。

7. 藥物交互作用

7.1 單胺氧化酶抑制劑

Linezolid 為一可逆性，不具選擇性的單胺氧化酶抑制劑(參閱禁忌(4.2)和臨床藥理學(12.3))。

7.2 腎上腺素類與血清素類藥物

linezolid 與腎上腺素類(adrenergic)和血清素類(serotonergic)藥物之間會有交互作用的可能性(參閱警語及注意事項(5.3); 5.6)，臨床藥理學(12.3))。

8. 特定族群使用

8.1. 懷 孕

致畸性

懷孕用藥級數 C：

小鼠、大鼠或兔子接受是人體暴露量 6.5 倍(小鼠)、等於(大鼠)或 0.06 倍(兔子)的 linezolid 劑量(根據 AUC 計算)時，並沒有致畸性；然而曾觀察到胚胎及胎兒的毒性(參閱非致畸性影響)，尚無充分且有良好對照，以孕婦為試驗對象的試驗，僅有在益處大於對胎兒的危險時，孕婦才可以接受 ZYVOX 的治療。

非致畸性影響

在小鼠，僅有在使用的劑量會造成母體毒性時(出現臨床徵狀和體重增加之趨勢減少)，才會觀察到對胚胎及胎兒的毒性。使用 450mg/kg/day 的劑量(根據 AUC 計算，相當於人體暴露量的 6.5 倍)會增加著床後胚胎的死亡，其中包括總窩數減少，胎兒體重減輕和增加肋骨之軟骨融合的發生率。

在大鼠，使用 15 和 50 mg/kg/day 劑量(根據 AUC 計算，相當於人體暴露量的 0.22 倍)時，會觀察到輕微的胎兒毒性。這些影響包括胎兒體重減輕、降低胸骨的骨化程度(此現象與胎兒體重減輕有關)。使用 50 mg/kg/day 劑量時，母體會產生體重增加趨勢減少的輕微毒性。

在兔子，劑量為 15 mg/kg/day (根據 AUC 計算，相當於人體暴露量的 0.06 倍)時，胎兒體重減輕只在有母體毒性(有臨床徵候、體重增加趨勢及食物消耗量減少等現象)時發生。

當雌大鼠在懷孕及授乳期間投與 linezolid 50 mg/kg/day 劑量(根據 AUC 計算，相當於人體暴露量)時，在產後 1 至 4 天，新生兒的存活率會降低。當新生鼠長大至有生育能力並進行交配時，發現有著床失敗率增加的現象。

8.3. 授乳

Linezolid 和它的代謝物會分泌至授乳大鼠的乳汁中。乳汁中的藥品濃度與母體血漿中的濃度相同。尚不知道 linezolid 是否會分泌至人的乳汁中，因為許多藥物分泌至乳汁中，因此授乳婦女在接受 ZYVOX 時應小心。

8.4. 兒童使用

從充分且有良好對照的成人臨床試驗、兒童病人的藥動學資料，以及對出生至 11 歲兒童病人所做的革蘭氏陽性菌感染對照研究得到的證據，足以證明 ZYVOX 用於兒童病人治療下列感染症有其安全性和有效性(參閱適應症(1)、臨床藥理學(12.3)與臨床研究(14))：

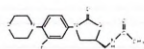
- 院內感染肺炎
- 複雜性皮膚和皮膚組織感染
- 社區感染型肺炎(對 8 個月至 12 歲兒童病人所做的非對照研究得到的證據也加以證實)
- 對 vancomycin 有抗藥性的 *Enterococcus faecium* 感染

對 5 到 17 歲兒童病人所做的對照研究已確立 ZYVOX 用於兒童病人治療下列感染症的安全性和有效性(參閱臨床研究)：

13

11. 簡介

ZYVOX 錠劑內含 linezolid，linezolid 是一種經合成、屬於 oxazolidinone 類的抗菌劑。Linezolid 的化學名為 (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide。Linezolid 的實驗式為 $C_{16}H_{20}FN_3O_4$ ，它的分子量是 337.35，其化學結構式如下：



ZYVOX 錠劑供口服投與的 600 毫克 linezolid，是一種衣膠錠，錠形形為 Corn starch, Microcrystalline cellulose, Hydroxypropyl cellulose, Purified water, Sodium starch glycolate, Carnauba wax, Isopropyl alcohol, Magnesium stearate, Opacode red S-1-15118, Opadry white YS-1-18202-A。600 毫克錠的鈉離子(Na⁺)含量為 2.92 毫克(每錠所含的鈉離子均為 0.1mEq)。

12. 臨床藥理學

12.1. 作用機轉

Linezolid 是一種抗生素(參閱微生物學)(12.4)。

12.2 藥效學

在一項隨機分組、以陽性藥物及安慰劑進行對照、並採交叉設計的完整 QT 研究中，對 40 位健康受試者投予單劑 ZYVOX 600 毫克(1 小時 IV 輸注)、單劑 ZYVOX 1200 毫克(1 小時 IV 輸注)、安慰劑、以及單劑陽性對照藥物(口服)。在 600 毫克及 1200 毫克的 ZYVOX 劑量下，達尖峰血中濃度時或在任何其它時間點中，皆未發現任何明顯的 QTc 間期影響。

12.3 藥動學

成人單次和多次口服及靜脈注射 linezolid 後的平均藥動學參數摘錄於表八。每 12 小時口服 600 毫克劑量後達穩定狀態時，linezolid 的血漿濃度如圖一所示。

表八：成人的 Linezolid 平均(標準差)藥動學參數

- 由 *Staphylococcus aureus*(僅限於對 methicillin 有感受性的菌株)或 *Streptococcus pyogenes* 引起的非複雜性皮膚和皮膚組織感染

藉由腦室腹腔分流術得到兒童病人給予單次和多次劑量之 Linezolid 後之藥物動力學資訊，顯示其於後腦脊液濃度是多變而不恆定的，無法達到或維持 Linezolid 之治療濃度之效果。因此，在經驗式治療之藥物選擇中並不建議將 Linezolid 用於中樞神經系統感染之兒童病人。

從出生至 17 歲兒童病人中其 linezolid 藥物動力學已評估過。在一般情況下，以體重為基礎的 linezolid 清除率隨著兒童病人年齡上升而逐漸降低。然而，在早產(孕齡小於 34 週)新生兒小於 7 天齡，其 linezolid 清除率通常比在足月新生兒小於 7 天齡還低。因此，早產兒小於 7 日齡時可能需要每 12 小時 10 毫克/公斤的替代給藥方案[用法用量 (2) 和臨床藥理學 (12.3)]。

有限的臨床經驗顯示，6 名受到革蘭氏陽性菌感染而接受 ZYVOX 治療(最小抑制濃度 MIC 為 4μg/mL)的兒童病人有 5 人(83%)在臨床痊愈。然而與成人相比，兒童病人 linezolid 的廓清率和全身暴露量(AUC)在受試者之間的差異比較大。對於臨床治療反應不佳的兒童病人，特別是病原菌 MIC 為 4μg/mL 的病人，評估臨床反應時應考慮全身暴露量較低、感染的部位及嚴重程度和原有疾病等問題(參閱臨床藥理學(12.3)和用法用量(2))。

8.5. 老年人使用

在第三期的對照臨床試驗中有 2046 名病人接受 ZYVOX 的治療，其中 65 歲或以上者有 589 人(29%)，75 歲或以上者有 253 人(12%)，這些老年病人和較年輕的病人比較時，在安全性及有效性整體上並無差異，其他已發表的臨床經驗也未發現老年人和年輕病人之間的治療反應具有差異，但未能排除某些具有較高的敏感性之老年病人。

10. 過量

過量時，建議採取支持性療法，並維持腎小球的過濾功能。血液透析可以促使 linezolid 加速排出。第一期臨床試驗中，投與 linezolid 三小時後開始進行為期三小時的透析時，約有 30% 的劑量會被排出。尚未有有關使用腹膜透析或血液灌流移除 linezolid 的資料。動物試驗中，大鼠接受 3000mg/kg/day 的劑量時，出現急性中毒的臨床症狀為活動降低和運動失調；狗接受 2000mg/kg/day 的劑量時，出現急性中毒的臨床症狀為嘔吐和衰弱。

14

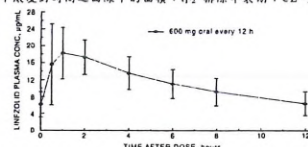
Linezolid 的劑量	C _{max} μg/mL	C _{min} μg/mL	T _{max} Hrs	AUC* μg · h/mL	t _{1/2} hrs	CL mL/min
600mg 錠劑						
單一劑量	12.70 (3.96)	---	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
每 12 小時	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600mg 靜脈注射						
單一劑量	12.90 (1.60)	---	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
每 12 小時	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)
600mg 口服懸浮劑						
單一劑量	11.00 (2.76)	---	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)

* 單一劑量的 AUC=AUC_{0-∞}；多劑量 AUC=AUC_{0-12h}

† 由 625mg 劑量標準化而得的數據；靜脈注射的劑量是以 0.5 小時輸注。

C_{max}=血中濃度最高值；C_{min}=血中濃度最低值；T_{max}=達到血中濃度最高值的時間

AUC=血中濃度對時間之曲線下的面積；t_{1/2}=排除半衰期；CL=全身廓清率。



圖一：成人每 12 小時口服 600 毫克的劑量後，在穩定狀態時，linezolid 的血漿濃度(平均值±標準差，n=16)

吸 收：Linezolid 口服後吸收完全。服藥後大約一至二小時可達到最高血漿濃度，其絕對生物可用率大約為 100%。因此 linezolid 可以口服或靜脈投與，無須調整劑量。

Linezolid 投與時不必考慮用餐時間的影響。當 linezolid 與高脂肪食物併用時，達到最

高血漿濃度的時間會延後 1.5 小時至 2.2 小時，而且血中濃度最高值會降低約 17%。然而這二種情況的時間由零至無限大之曲線下濃度總面積(AUC_{0-∞})相似。

分佈：動物及人體的藥動學研究顯示 linezolid 容易分佈至高血液灌輸的組織。Linezolid 的蛋白質結合率大約為 31%，此結合率與藥品的濃度高低無關。在健康的成人自願受試者，linezolid 在穩定狀態時的分佈體積平均為 40 至 50 公升。

從數目有限，參與第一期臨床試驗的受試者在多次投與 linezolid 後，測出 linezolid 在不同體液中的濃度。Linezolid 在唾液與血漿中的濃度比率為 1.2 比 1，在汗液與血漿中的濃度比率為 0.55 比 1。

代謝：Linezolid 的主要代謝途徑為 morpholine 環的氧化，這產生兩個非活性，環型結構打開的羧酸(carboxylic acid)代謝物：aminoethoxyacetic acid 代謝物(A)和 hydroxyethyl glycine 代謝物(B)。據推測，代謝物 A 的形成是經由酵素途徑形成的，而代謝物 B 的形成主要是經由體外一種不需酵素催化的化學氧化機制。體外試驗證明 linezolid 很少被代謝，可能是經由人體細胞色素 P450 代謝催化的。然而，linezolid 的代謝途徑尚未完全明瞭。

排泄：非腎臟廓清率大約占 linezolid 全身廓清率的 65%。在穩定狀態時，大約有 30% 的劑量以 linezolid 形態出現在尿液中，而有 40% 的劑量以代謝物 B 及 10% 的劑量以代謝物 A 形態出現在尿液中。腎臟的平均廓清率為 40 毫升/分鐘，暗示有腎小管再吸收的現象。實際上並未有 linezolid 出現在糞便中，然而有 6% 及 3% 的劑量分別以代謝物 B 及代謝物 A 出現在糞便中。

增加 linezolid 的劑量時，觀察到廓清率有小幅度的非線性現象，這可能是由於在較高濃度時，linezolid 腎臟和非腎臟廓清率較低。然而這廓清率的差異很小，並不影響其排除半衰期。

特殊族群

老年病人：老年病人(65 歲或以上)的藥動學沒有顯著的改變，因此老年病人不需要調整劑量。

兒童病人：曾對出生至 17 歲的兒童病人(包括早產和足月產嬰兒)，12 歲至 17 歲的健康青少年，以及 1 週到 12 歲的兒童病人中調查 linezolid 靜脈注射單一劑量後的藥動學。兒童族群及健康成人受試者靜脈注射單一劑量後，linezolid 藥動學參數摘錄於表

(N=36)	[9.9, 28.9]	[0.44, 0.79]	[32, 178]	[1.3, 8.1]	[0.9, 5.2]
成人受試者 [‡]	12.5 (21%)	0.65 (16%)	91 (33%)	4.9 (35%)	1.7 (34%)
(N=29)	[8.2, 19.3]	[0.45, 0.84]	[53, 155]	[1.8, 8.3]	[0.9, 3.3]

* AUC=單一劑量 AUC_{0-∞}。

** 這組數據中，「早產」被定義為孕齡<34 週(注意：只有一名入選的早產兒年齡介於 1 週至 28 天之間)。

*** 在這組數據中，「足月產」被定義為孕齡≥34 週。

[‡] 10mg/kg 之劑量。

[§] 600mg 或 10mg/kg 直到最高劑量 600mg。

[§] 劑量標準化至 600mg。

C_{max}=血中濃度最高值；V_d=分佈體積；AUC=血中濃度對時間之曲線下的面積；t_{1/2}=排除半衰期；CL=以體重標準化之全身廓清率。

性別：女性 linezolid 的分佈體積比男性稍低。血漿濃度女性比男性高，部份原因可能是由於體重的差異。投與 600 毫克的劑量後，女性的平均口服廓清率比男性大約低 38%；然而關於排除速率常數或半衰期，並無顯著的性別差異。因此，於是女性病人在接受藥物治療時，並不預期血中濃度會大量增加超過可耐受的限度。所以，不同性別者並不需要調整劑量。

腎功能不全：對於不同程度腎功能不全的病人，linezolid 原形藥物的藥動學並不會改變；然而，在腎功能不全的病人，二個主要的 linezolid 代謝物有蓄積的現象，蓄積的量隨腎功能不全的嚴重度增加而增加(參閱表十)。對末期腎病並接受血液透析治療的病人，進行 linezolid 與其兩項代謝物的藥物動力學試驗。末期腎病病人試驗中，14 名病人接受每 12 小時 linezolid 600 mg，共 14.5 天的治療(參閱表十一)。因為不管腎功能如何，均可達到相近的 linezolid 的血漿濃度，所以對於腎功能不全的病人不建議要調整劑量。然而，因為缺乏關於這些主要代謝物蓄積所代表的臨床意義的資訊，腎功能不全病人使用 linezolid 時，須衡量這些代謝物蓄積時所造成的潛在危險性。Linezolid 和二個代謝物可藉由血液透析方法排除。尚未有有關腹膜透析對 linezolid 藥動學之影響的資料，投與 linezolid 三小時後開始進行為期三小時的血液透析時，約有 30% 的劑量會被排出，因此 linezolid 應在血液透析後才投與。

表十：在各種嚴重程度的腎功能不全病人中，口服投與單一劑量 600mg linezolid 後，Linezolid 和代謝物 A 和 B 的平均(標準差)AUC 和排除半衰期

參數	健康受試者	中度腎功能不全	重度腎功能不全
CL _{CR} > 80 mL/min		30 < CL _{CR} < 80 mL/min	10 < CL _{CR} < 30 mL/min

九。

兒童病人不管年紀為何，linezolid 的血中濃度最高值(C_{max})和分佈體積(V_d)都相似；然而 linezolid 的血漿廓清率會隨著年齡的增加而改變。除了年紀未滿一週的早產新生兒之外，年紀最小的一組(小於 1 週至 11 歲)其基於體重的廓清率最快，所以單一劑量全身暴露量(AUC)比成人低，半衰期也比較短。當兒童病人族群之年齡增加時，linezolid 根據體重的廓清率便隨之降低，到青春前期，平均廓清率的數值就接近成人族群了。各小兒科年齡組的 linezolid 廓清率 and 全身暴露量(AUC)的個別差異都比成人大。

在從出生至 11 歲的兒童病人中，每 8 小時投與一次得到的平均每日 AUC 值，與在青少年及成人中，每 12 小時投與一次得到的 AUC 值相似。因此 11 歲以下兒童病人的劑量應該是每 8 小時服用 10mg/kg；12 歲或年紀更大的兒童病人，劑量應該是每 12 小時服用 600 mg (參閱用法用量)。

表九：兒童與成人靜脈注射單一劑量 10mg/kg 或 600mg linezolid 之後，linezolid 的藥動學參數(平均：(%CV)；[最小值，最大值])

年齡層	C _{max} μg/mL	V _{ss} L/kg	AUC ^a μg · h/mL	t _{1/2} hrs	CL mL/min/kg
新生兒病人					
早產**	12.7 (30%)	0.81 (24%)	108 (47%)	5.6 (46%)	2.0 (52%)
<1週(N=9) [†]	[9.6, 22.2]	[0.43, 1.05]	[41, 191]	[2.4, 9.8]	[0.9, 4.0]
足月產***	11.5 (24%)	0.78 (20%)	55 (47%)	3.0 (55%)	3.8 (55%)
<1週(N=10) [†]	[8.0, 18.3]	[0.45, 0.96]	[19, 103]	[1.3, 6.1]	[1.5, 8.8]
足月產***					
≥1週至≤28天	12.9 (28%)	0.66 (29%)	34 (21%)	1.5 (17%)	5.1 (22%)
(N=10) [†]	[7.7, 21.6]	[0.35, 1.06]	[23, 50]	[1.2, 1.9]	[3.3, 7.2]
嬰兒病人					
>28天至≤3個月	11.0 (27%)	0.79 (26%)	33 (26%)	1.8 (28%)	5.4 (32%)
(N=12) [†]	[7.2, 18.0]	[0.42, 1.08]	[17, 48]	[1.2, 2.8]	[3.5, 9.9]
兒童病人					
3個月至11歲 [†]	15.1 (30%)	0.69 (28%)	58 (54%)	2.9 (53%)	3.8 (53%)
(N=59)	[6.8, 36.7]	[0.31, 1.50]	[19, 153]	[0.9, 8.0]	[1.0, 8.5]
青少年受試者與病人					
12歲至17歲 [‡]	16.7 (24%)	0.61 (15%)	95 (44%)	4.1 (46%)	2.1 (53%)

Linezolid			
AUC _{0-∞} , μg h/mL	110(22)	128(53)	127(66)
t _{1/2} , 小時	6.4(2.2)	6.1(1.7)	7.1(3.7)
代謝物 A			
AUC ₀₋₁₂ , μg h/mL	7.6(1.9)	11.7(4.3)	56.5(30.6)
t _{1/2} , 小時	6.3(2.1)	6.6(2.3)	9.0(4.6)
代謝物 B ¹			
AUC ₀₋₁₂ , μg h/mL	30.5(6.2)	51.1(38.5)	203(92)
t _{1/2} , 小時	6.6(2.7)	9.9(7.4)	11.0(3.9)

¹ 代謝物 B 是 Linezolid 的主要代謝物。

表十一：在末期腎病的受試者中，接受每 12 小時 linezolid 600 mg，共 14.5 天的治療後，Linezolid 和代謝物 A 和 B 的平均(標準差)AUC 和排除半衰期

參數	末期腎病受試者 ¹
LINEZOLID	
AUC ₀₋₁₂ , μg h/mL (最後一劑藥物後)	181 (52.3)
t _{1/2} , 小時 (最後一劑藥物後)	8.3 (2.4)
代謝物 A	
AUC ₀₋₁₂ , μg h/mL (最後一劑藥物後)	153 (40.6)
t _{1/2} , 小時 (最後一劑藥物後)	15.9 (8.5)
代謝物 B ²	
AUC ₀₋₁₂ , μg h/mL (最後一劑藥物後)	356 (99.7)
t _{1/2} , 小時 (最後一劑藥物後)	34.8 (23.1)

¹ 兩次透析之間

² 代謝物 B 為 linezolid 的主要代謝物。

肝功能不全：輕度至中度肝功能不全(Child-Pugh class A 或 B)病人(n=7)的 linezolid 藥動學並不會改變。根據現有的資料，對於輕度至中度肝功能不全病人，並不建議要調整劑量。嚴重肝功能不全病人的 linezolid 藥動學尚未被評估。

藥物交互作用

藉由細胞色素 P450 代謝的藥物

在大鼠，linezolid 不是細胞色素 P450 (CYP450)的誘導劑。此外，linezolid 不會抑制具臨床重要性的人體 CYP isoforms (如 1A2, 2C9, 2C19, 2D6, 2E1, 3A4)的活性。(S)-warfarin 主要是由 CYP2C9 代謝，linezolid 與(S)-warfarin 併用時，並不會明顯改變(S)-warfarin 的藥動學特性。藉由 CYP2C9 代謝的藥物如 warfarin 和 phenytoin，與 linezolid 併用時並不需要調整劑量。

抗生素

Aztreonam：當 aztreonam 與 linezolid 併用時，linezolid 或 aztreonam 的藥動學均不會改變。

Gentamicin：當 gentamicin 與 linezolid 併用時，linezolid 或 gentamicin 的藥動學均不會改變。

抗氧化劑

對健康的自願受試者，進行 linezolid 與抗氧化劑維生素 C 與維生素 E 之間，藥物交互作用的可能性試驗。受試者在第 1 天口服 linezolid 600 mg，接著在第 8 天口服另一劑 linezolid 600 mg。在第 2-9 天，投與受試者維生素 C (1000 mg/day)或維生素 E (800 IU/day)。Linezolid 的 AUC_{0-∞}，併用維生素 C 時增加 2.3%，併用維生素 E 時增加 10.9%，併用維生素 C 或維生素 E 時，不建議調整 linezolid 的劑量。

強效 CYP3A4 誘導劑

Rifampin：曾針對 16 位健康成年男性志願者進行的一項研究，每天投予兩次 linezolid 600 毫克共 5 劑，合併或合併 rifampin 600 毫克每天投予一次連續 8 天，藉以評估 rifampin 對 linezolid 之藥物動力學的影響。併用 rifampin 和 linezolid 會使 linezolid 的 C_{max} 降低 21% [90% CI, 15%-27%]，AUC 降低 32% [90% CI, 27%-37%]。此交互作用的臨床意義尚不明確。目前尚未完全明瞭此交互作用的發生機制，可能與誘導肝臟酵素(如細胞色素 P450)有關。其他肝臟酵素強誘導劑(如 carbamazepine、phenytoin、phenobarbital)可能引起幅度類似或較小的 linezolid 暴露量降低。

單胺氧化酶(Monoamine Oxidase)抑制劑

Linezolid 為一可逆性，不具選擇性的單胺氧化酶抑制劑。因此，linezolid 與腎上腺素類(adrenergic)和血清素類(serotonergic)藥物之間可能會交互作用。

腎上腺素類(adrenergic)藥物

一些接受 ZYVOX 的人，會可逆性地增加經間接作用而產生效果的交感神經興奮劑、昇壓劑或多巴胺藥物的血壓上升作用。常用的藥物如 phenylpropanolamine 和 pseudophedrine 已經被特別的研究。腎上腺素類藥物如 dopamine 或 epinephrine 的起

始劑量應該降低，並且調整至能產生所要反應的劑量。

Tyramine：正常成年人同時接受 linezolid 及劑量高於 100 毫克的酪胺(tyramine)時會產生明顯的血壓上升反應。因此，接受 linezolid 治療的病人應避免大量食用含高酪胺的食物或飲料(參閱病人資訊(16))。

Pseudoephedrine HCl 或 phenylpropanolamine HCl：當健康、血壓正常的受試者接受 linezolid 時，會加強 pseudoephedrine HCl (PSE)或 phenylpropanolamine HCl (PPA) 的升壓上反應，這血壓的增高是可逆性的(參閱警語及注意事項(5.6)，藥物交互作用(7))。類似的試驗並未在高血壓病人身上進行。以血壓正常者為受試者的交互作用試驗中，測量安樂劑、單獨使用 PPA 或 PSE、單獨使用 linezolid、以及在 linezolid 達穩定狀態時(每 12 小時服用 600 毫克，使用三天) 併用二個劑量的 PPA(25mg)或 PSE (60mg)(隔四小時服用)等情況時對血壓和心跳速率的影響。任何一種治療方式都不會影響心跳速率。Linezolid 併用 PPA 或 PSE 的治療方式會使血壓升高，最高的血壓出現在使用第二個 PPA 或 PSE 劑量後的 2 至 3 小時，並於出現最高的血壓後 2 至 3 小時回到基線值。關於 PPA 的研究結果如下：平均(和範圍)最高收縮壓(單位:mmHg)：安樂劑組= 121(103 至 158)；單獨使用 linezolid 組= 120(107 至 135)，單獨使用 PPA = 125(106 至 139)；PPA 併用 linezolid 組= 147(129 至 176)。PSE 的研究結果和 PPA 的研究結果相似，linezolid 與 pseudoephedrine 或 phenylpropanolamine 併用後，與基線值比較時，平均最大收縮壓增加的數值分別為 32 mmHg (範圍：20-52 mmHg)及 38 mmHg (範圍：18-79 mmHg)。

血清素類(serotonergic)藥物

Dextromethorphan：曾以健康受試者評估 linezolid 與 dextromethorphan 之間的交互作用。受試者單獨服用 dextromethorphan (每次投與 20mg，投與二次，之間間隔 4 小時)或併用 dextromethorphan 與 linezolid。健康受試者同時併用 dextromethorphan 與 linezolid 時，並沒有出現血清素症候群(serotonin syndrome)(混亂、譫妄、心神不定、震顫、臉紅、發汗和過高熱)。

12.4 微生物學

作用機轉

Linezolid 是一種人工合成的抗生素，屬於 oxazolidinone 類，它的臨床用途主要是治療嗜氧性革蘭氏陽性菌所造成的感染。體外試驗亦顯示 linezolid 對一些革蘭氏陰性菌和厭氧菌有作用。Linezolid 會與細菌 50S 核糖小體(subunit)上的 23S 核糖 RNA 結合，並阻止功能性的 70S 起始複合體的形成。此複合體是細菌繁殖過程中必要的物質。時間殺死(time-kill)的研究結果顯示，對腸球菌屬(enterococci)和葡萄球菌屬(staphylococci)而言，linezolid 是抑菌劑(bacteriostatic)。對鏈球菌屬(streptococci)大多數的分離菌株而

言，linezolid 是殺菌劑(bactericidal)。

抗藥性機轉

體外試驗顯示，23S rRNA 的單點突變(point mutation)與 linezolid 的抗藥性有關。有報告指出，在臨床使用 linezolid 期間，vancomycin 抗藥性 *Enterococcus faecium* 對 linezolid 產生了抗藥性。有報告指出，在臨床使用 linezolid 期間，methicillin 抗藥性金黃色葡萄球菌(*Staphylococcus aureus*)對 linezolid 產生了抗藥性。這些細菌對 linezolid 的抗藥性都與細菌 23S rRNA 的單點突變(在 2576 位置上以胸腺嘧啶[thymine]取代鳥嘌呤[guanine])有關。由於編碼 23S rRNA 或核糖體蛋白(L3 和 L4)的染色體基因出現突變而對 oxazolidinone 類藥物具有抗藥性的微生物，通常對 linezolid 具有交叉抗藥性。此外，甲基轉移酶也會媒介葡萄球菌的 linezolid 抗藥性。此抗藥性由位於質體內的 *cfr* (chloramphenicol-florfenicol)基因媒介，質體能在葡萄球菌之間傳遞。

與其他抗微生物藥物的交互作用

體外試驗已研究發現 linezolid 與 vancomycin, gentamicin, rifampin, imipenem-cilastatin, aztreonam, ampicillin 或 streptomycin 之間有加成作用 (additivity) 或無關性 (indifference)。

在體外試驗或臨床上的感染，linezolid 能有效的對抗下列微生物的分離菌株(isolate) (參閱適應症(1))。

革蘭氏陽性菌

Enterococcus faecium (僅限於對 vancomycin 有抗藥性的分離菌株)

Staphylococcus aureus (包括對 methicillin 有抗藥性的分離菌株)

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

下列所述有體外試驗的資料可參考，但其實際的臨床重要性尚不清楚。超過 90% 的下列細菌顯示的體外最小抑菌濃度(MIC)低於或等於表 12-2 中所示類似屬微生物的 linezolid 感受性臨界點(linezolid-susceptible breakpoint)。Linezolid 用於治療這些細菌所造成之臨床感染的安全性和有效性，尚未經由適當的及有良好對照組的臨床試驗證實。

革蘭氏陽性菌

Enterococcus faecalis (包括對 vancomycin 有抗藥性的分離菌株)

Enterococcus faecium (對 vancomycin 有感受性的分離菌株)

Staphylococcus epidermidis (包括對 methicillin 有抗藥性的分離菌株)

Staphylococcus haemolyticus

Viridans group streptococci

革蘭氏陰性菌

Pasteurella multocida

敏感性(Susceptibility)試驗方法

有關本藥品經美國食品藥物管理局認可之藥物敏感性測試規範，以及相關測試方法及品質控制標準，請參閱 <https://www.fda.gov/STIC>。當有結果時，臨床微生物學實驗室應將當地醫院及執業場所所用抗生素產品的體外試驗的感受性試驗結果以定期報告的方式提供給醫師參考。報告內容應包括院內感染菌種和社區型感染病原菌的感受性情形。這些報告將有助於醫師選用抗生素產品以進行治療。

將藥物以一定量分佈於以一定量之細菌培養液(如 vancomycin inhibitory concentration - MIC)此藥之抑制濃度不同於評估如藥物對在基質中感受性。以在基質中感受性時評估為標準方法。此表格之說明書，應由藥師或藥師之助理人員在臨床使用時參考。

將藥物以一定量分佈於以一定量之細菌培養液(如 vancomycin inhibitory concentration - MIC)此藥之抑制濃度不同於評估如藥物對在基質中感受性。以在基質中感受性時評估為標準方法。此表格之說明書，應由藥師或藥師之助理人員在臨床使用時參考。

表 12-2 Linezolid 的敏感性和 MIC 值

藥名	最低抑菌濃度					
	MIC 值 (μg/ml)			折斷指數		
	5	5	5	5	5	5
<i>Enterococcus faecium</i> - 敏感	≤ 2	4	≤ 8	≤ 24	≤ 24	≤ 24
<i>Staphylococcus aureus</i> - 敏感	≤ 4	—	≤ 8	≤ 24	—	≤ 24
<i>Streptococcus pneumoniae</i> - 敏感	≤ 2	—	—	≤ 24	—	—
<i>Streptococcus pneumoniae</i> - 敏感	≤ 2	—	—	≤ 24	—	—

5 = 感受性，1 = 中度感受性，2 = 抗藥性

a - 以紙板擴散法對葡萄球菌屬物種進行測試時，應將培養皿面向光源，利用穿透的光線進行判讀。其土沒有任何明顯，可以肉眼直接觀察到之菌生長現象的區域，即應視為葡萄菌菌落。請參閱表格

細菌培養—必須使用放大鏡才能觀察到的細菌培養—細菌培養內若有任何可辨識的細菌生長跡象—即代表存在抗藥性—以紙錠培養法獲得的抗藥性結果—應以MIC法進行確認—

b-給予感受性(susceptible)這一分類外—現在並沒有任何關於其抗藥性分類的任何資料—所以無法定義其他分類的標準—分藥藥物的試驗(yielding-test)結果若顯示為非感受性(non-susceptible)這一分類時—應重新測試—倘若結果確認為非感受性—則應將此分藥藥物(isolate)送至鑑定實驗室進一步測試—

非感受性(non-susceptible)的分類應與非感受性分類的微生物學培養結果相一致—如果微生物學培養結果顯示為非感受性(non-susceptible)—而分藥藥物試驗結果顯示為感受性—則應將此分藥藥物送至鑑定實驗室進一步測試—如果微生物學培養結果顯示為感受性—而分藥藥物試驗結果顯示為非感受性—則應將此分藥藥物送至鑑定實驗室進一步測試—

品質管制

非感受性的分藥藥物應與非感受性分類的微生物學培養結果相一致—如果微生物學培養結果顯示為非感受性—而分藥藥物試驗結果顯示為感受性—則應將此分藥藥物送至鑑定實驗室進一步測試—如果微生物學培養結果顯示為感受性—而分藥藥物試驗結果顯示為非感受性—則應將此分藥藥物送至鑑定實驗室進一步測試—

分藥藥物名稱	非感受性的分藥藥物結果	非感受性的分藥藥物結果
	給予分藥藥物結果	紙錠培養法結果
	紙錠培養法結果	紙錠培養法結果
<i>Enterococcus faecalis</i> ATCC-29222	1-4	不適用
<i>Staphylococcus aureus</i> ATCC-29222	1-4	不適用
<i>Staphylococcus aureus</i> ATCC-29222	不適用	16-32
<i>Streptococcus pneumoniae</i> ATCC-49463	1-2-3	16-32

a-重測試—*Streptococcus pneumoniae* 以外的 *Streptococcus* 屬時—此菌種可用於感受性試驗結果的確認試驗—

13. 非臨床毒物學

13.1 致癌性、致突變性及對生殖功能的傷害雖然尚未進行動物終身的研究以評估 linezolid 的致癌能力，但是根據一綜合試驗包括致突變性分析法(Ames 細菌隔代遺傳及 CHO 細胞突變)、體外 unscheduled DNA synthesis(UDS)分析法、人體淋巴球的體外染色體異常(chromosome aberration)分析法和體內小鼠核(micronucleus)測試法，linezolid 並不會有致突變性或使染色體斷裂(clastogenic)。

床試驗的受試者。受試者接受 7 至 21 天的治療。其中一組接受 ZYVOX 靜脈注射劑 600mg、每 12 小時一次；另一組接受 vancomycin 1g 靜脈注射、每 12 小時一次。二組同時併用 aztreonam (1 至 2g 靜脈注射、每 8 小時一次)，如果臨床上需要，可以繼續併用。203 名接受 linezolid 治療的病人和 193 名接受 vancomycin 治療的病人進入本試驗。接受 linezolid 治療者有 122 人(60%)是臨床上可評估的；而接受 vancomycin 治療者有 103 人(53%)是臨床上可評估的。臨床上可評估的受試者中，接受 linezolid 治療者之治癒率為 57%，而接受 vancomycin 治療者之治癒率為 60%。臨床上可評估的受試者中，因呼吸器造成的肺炎之治癒率在接受 linezolid 治療者為 47%，而接受 vancomycin 治療者為 40%。94 名接受 linezolid 治療的病人和 83 名接受 vancomycin 治療的病人符合修正型意圖治療(modified intent-to-treat, MITT)分析。這些病人在開始治療前，已經分離出病原菌。依 MITT 分析而得的治癒率在接受 linezolid 治療者為 57%，而接受 vancomycin 治療者為 46%。表十三^{三三}為微生物學上可評估的受試者中，依病原菌之治癒率。

表十三^{三三}：微生物學上可評估的院內肺炎成人病人在 Test-of-Cure 診察時的治癒率

病原體	治癒率	
	ZYVOX n/N (%)	Vancomycin n/N (%)
<i>Staphylococcus aureus</i>	23/38 (61)	14/23 (61)
Meticillin-抗藥性 <i>S. aureus</i>	13/22 (59)	7/10 (70)
<i>Streptococcus pneumoniae</i>	9/9 (100)	9/10 (90)

複雜性皮膚和皮膚組織感染

經由臨床上證實之成年複雜性皮膚和皮膚組織感染病人被選為一隨機、多試驗中心、雙盲、double-dummy 臨床試驗的受試者。本試驗比較試驗藥品在光給與靜脈注射劑後，再給與口服藥品的情形，整個治療時間為 10 至 21 天。其中一組先接受 ZYVOX 靜脈注射劑 600 毫克、每 12 小時一次，之後改為 ZYVOX 口服錠劑 600mg、每 12 小時一次；另一組先接受 oxacillin 2 克靜脈注射、每 6 小時一次，之後改為口服 dicloxacillin 500 毫克、每 6 小時一次。如果臨床上需要，可以併用 aztreonam。400 名接受 linezolid 治療的病人和 419 名接受 oxacillin 治療的病人進入本試驗。接受 linezolid 治療者有 245 人(61%)是臨床上可評估的；而接受 oxacillin 治療者有 242 人(58%)是臨床上可評估的。臨床上可評估的病人的治癒率，接受 linezolid 者為 90%，而接受 oxacillin 者為 85%。修正型意圖治療(MITT)分析包含 316 名接受 linezolid 治療的病人和 313 名接受 oxacillin 治療的病人。這些病人符合進入本試驗的所有規定。依 MITT 分析而得

Linezolid 不會影響成年雌性大鼠的生殖力或生育功能。當給與 linezolid 的劑量 $\geq 50\text{mg/kg/day}$ 時(暴露量大約等於或大於人體暴露量，此乃根據 AUC 來作比較)，成年雌性大鼠會可逆性地降低生殖力或生育功能。這種作用是經由改變精子生成造成的。被影響的精細胞含有形成異常及取向(orientation)異常的粒線體，不能存活。生殖力降低可能導致副睪上皮細胞肥大(epithelial cell hypertrophy)及增生。在狗身上並未見到類似的副睪改變。

幼年雄性大鼠在性器官發育期給與 linezolid(第 7 至 36 天大時給與 linezolid 50mg/kg/day；第 37 至 55 天大時給與 linezolid 100mg/kg/day；此暴露量比 3 個月至 11 歲兒童病人的平均 AUC 大 1.7 倍)，到成熟時生殖力會輕微的降低，自胎兒仍在子宮內直到新生兒期早期的暴露(妊娠第 6 天直到產後 5 天)、新生兒暴露(產後 5 至 21 天)或幼年暴露(產後 22 至 35 天)等短期治療並未觀察到生殖力降低的現象。在產後 22 至 35 天接受治療的大鼠身上觀察到可逆性的精子活動力降低，精子的形態也有改變。

13.2 動物毒理學和/或藥理學

在年輕和成年的大鼠及狗，linezolid 毒性的標靶器官類似。動物試驗中觀察到與劑量和使用時間相關的骨髓抑制作用，此經由產生骨髓細胞結構減少(hypocellularity)，造血功能降低，脾臟與肝臟的骨髓外造血功能降低，及循環系統中紅血球、白血球、血小板數目減少的現象證實。胸腺、淋巴結、脾臟發生類淋巴細胞缺乏，這種現象通常會伴隨厭食、體重減輕、體重增加減少，而這些因素可能與所觀察到的現象之成因亦有關。

在接受口服 linezolid 達 6 個月的大鼠中，觀察到接受 80 mg/kg/day 的雄大鼠出現不可逆的輕微至中度坐骨神經軸突退化之現象，在三個月期中屍體檢驗時也觀察到一隻接受此劑量的雄大鼠出現輕微的坐骨神經退化之現象。在雌大鼠未觀察到類似的變化。進行敏感的灌流固定之組織形態學評估，調查視神經退化的證據。給藥六個月之後，二隻雄大鼠顯然有輕微至中度視神經退化，但因該結果是急性的而且分佈不對稱，故其與藥物的直接關係並不確定。觀察到的神經退化在顯微鏡下與老化大鼠的自發性單側視神經退化一致，而且可能是一般背景變化加劇的結果。

這些作用是在與某些人類受試者接受相當的暴露量時被觀察到的。雖然一些試驗中，在後階段時，此症狀的回復並不完全，但是基本上此造血及淋巴樣系統所發生的影響是可逆的。

14. 臨床研究

14.1 成人院內感染的肺炎

經由臨床上和放射線學證實之成年院內肺炎病人被選為一隨機、多試驗中心、雙盲臨

的治癒率在接受 linezolid 治療者為 86%，而接受 oxacillin 治療者為 82%。表十三^{三三}列出微生物學上可評估的受試者中，依病原菌之治癒率。

表十三^{三三}：微生物學上可評估的成年複雜性皮膚和皮膚組織感染病人在 Test-of-Cure 診察時的治癒率

病原體	治癒率	
	ZYVOX n/N (%)	Oxacillin/Dicloxacillin n/N (%)
<i>Staphylococcus aureus</i>	73/83(88)	72/84(86)
Meticillin-抗藥性 <i>S. aureus</i>	2/3(67)	0/0(-)
<i>Streptococcus agalactiae</i>	6/6(100)	3/6(50)
<i>Streptococcus pyogenes</i>	18/26(69)	21/28(75)

另一個個別的研究提供 linezolid 用於治療 meticillin-抗藥性 *Staphylococcus aureus* (MRSA)感染的經驗。這是一個隨機開放性試驗，以證實或疑似 MRSA 感染的成年住院病人為受試者。

其中一組先接受 ZYVOX 靜脈注射劑 600mg、每 12 小時一次，之後改為 ZYVOX 口服錠劑 600mg、每 12 小時一次；另一組接受 vancomycin 1g 靜脈注射、每 12 小時一次。二組治療時間均為 7 至 28 天，如果臨床上需要，可以併用 aztreonam 或 gentamicin。微生物學上可評估的 MRSA 皮膚和皮膚組織感染病人的治癒率，接受 linezolid 治療者為 26/33(79%)，而接受 vancomycin 治療者為 24/33(73%)。

糖尿病足感染

經由臨床上證實之成年複雜性皮膚和皮膚組織感染(糖尿病足感染)的成年糖尿病病人被選為一隨機(二比一的比例)、多試驗中心、開放性臨床試驗的受試者。本試驗比較試驗藥品由靜脈注射或口服給與的情形，整個治療時間為 14 至 28 天。其中一組接受 ZYVOX 600 毫克靜脈注射或口服、每 12 小時一次；另一組接受 ampicillin/sulbactam 1.5 克至 3 克靜脈注射或 amoxicillin/clavulanate 500 毫克至 875 毫克口服、每 8 至 12 小時一次。在 ampicillin/sulbactam 未上市的國家，靜脈注射治療使用 amoxicillin/clavulanate 500 毫克至 2 克靜脈注射、每 6 小時一次。若從足部感染分離出 MRSA，對照組也可用 vancomycin 1 克靜脈注射、每 12 小時一次。若從感染部位分離出革蘭氏陰性菌，任一治療組的病人也可接受 aztreonam 1 克至 2 克靜脈注射、每 8 至 12 小時一次。所有的病人都有資格接受適當的輔助治療(例如清瘡及解除負荷[off-loading])，和一般治療糖尿病足感染時需要的一樣，結果大多數病人接受了這些治療。這個意圖治療(ITT)

研究群體包含 241 名接受 linezolid 治療的病人和 120 名接受對照品治療的病人。接受 linezolid 治療者有 212 人(86%)是临床上可評估的;而接受對照品治療者有 105 人(85%)是临床上可評估的。此 ITT 群體的治療率在接受 linezolid 治療者為 68.5%(165/241),而接受對照品治療者為 64%(77/120),結果有疏漏或未確定的受試者被視為治療失敗。临床上可評估的病人(排除結果遺失或未確定的受試者)的治療率,在接受 linezolid 治療者為 83%(159/192),而在接受對照品治療者為 73%(74/101)。一項關鍵事後分析(post-hoc analysis)以 121 名接受 linezolid 治療的病人和 60 名接受對照品治療的病人為對象,這些病人的感染部位或血液分離出革蘭氏陽性病原菌,而併發骨髓炎的證據比整個研究群體少,並且未接受被禁止的抗菌劑。據分析,治療率在接受 linezolid 治療者為 71%(86/121),而在接受對照品治療者為 63%(38/60)。上述分析皆未以輔助治療的使用加以校正。表十四列出從微生物學上可評估的受試者中,依病原菌之治療率。

表十四: 微生物學上可評估的成年糖尿病性足部感染病人在 Test-of-Cure 診察時的治療率

病原體	治 療 率	
	ZYVOX n/N (%)	對照品 n/N (%)
<i>Staphylococcus aureus</i>	49/63 (78)	20/29 (69)
Meticillin-抗藥性 <i>S. aureus</i>	12/17 (71)	2/3 (67)
<i>Streptococcus agalactide</i>	25/29 (86)	9/16 (56)

Vancomycin-抗藥性腸球菌(enterococcal)感染

證實或疑似由 vancomycin-抗藥性腸球菌感染的成人病人被選為一隨機、多試驗中心、雙盲臨床試驗的受試者,該試驗比較高劑量 ZYVOX (600mg 每 12 小時一次,靜脈注射或口服)和低劑量 ZYVOX (200mg 每 12 小時一次,靜脈注射或口服)治療 7 至 28 天的情形。病人可以同時併用 aztreonam 或 aminoglycoside。79 名病人被隨機分配至高劑量 linezolid 組,66 名病人被隨機分配至低劑量 linezolid 組。在基線經證實是 vancomycin-抗藥性腸球菌感染且符合意圖治療 (ITT)分析的病人,在高劑量組有 65 人,在低劑量組有 52 人。

在基線經證實是 vancomycin-抗藥性 enterococcal 感染且符合 intent-to-treat (ITT)分析之病人的治療率(cure rate)如表十五所列,該表是根據感染來源列出。這些治療率並不包括結果資料有疏漏或未確定的受試者。雖然按照 0.05 的水準並無統計學上顯著的差異,但是高劑量組的治療率比低劑量組的治療率高。

29

vancomycin 抗藥性之腸球菌的病人),依病原菌之治療率。

表十五: 意圖治療、修正意圖治療、及临床上可評估的兒童病人在治療試驗診察時的治療率 (針對整體族群,以及依特定基準診斷區分)

群體	ITT		MITT*		临床上可評估的	
	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)
任何診斷	150/186 (81)	69/83 (83)	86/108 (80)	44/49 (90)	106/117 (91)	49/54 (91)
複雜性皮膚與皮膚組織感染	61/72 (85)	31/34 (91)	37/43 (86)	22/23 (96)	46/49 (94)	26/27 (96)
院內的肺炎	13/18 (72)	11/12 (92)	5/6 (83)	4/4 (100)	7/7 (100)	5/5 (100)

* MITT = 基線時分離出革蘭氏陽性病原菌的 ITT 病人

表十六: 微生物學上可評估的革蘭氏陽性病原菌感染之兒童病人在治療試驗診察時的治療率

病原體	治 療 率	
	ZYVOX n/N (%)	Vancomycin n/N (%)
Vancomycin-抗藥性 <i>Enterococcus faecium</i>	6/8 (75)*	0/0 (-)
<i>Staphylococcus aureus</i>	36/38 (95)	23/24 (96)
Meticillin-抗藥性 <i>S. aureus</i>	16/17 (94)	9/9 (100)
<i>Streptococcus pyogenes</i>	2/2 (100)	1/2 (50)

*包括開放性延伸試驗中所收錄的 7 個病人資料。

15. 包裝

錠 劑 (本藥須由醫師處方使用)

600mg (白色、膠囊形狀之膜衣錠,表面印有“ZYVOX 600mg”)
100 錠 HDPE 瓶裝
20 錠 HDPE 瓶裝
30 錠 單一劑量包裝

表十七: 在基線經證實是由 vancomycin-抗藥性腸球菌感染且符合 ITT 分析之成人病人在 Test-of-Cure 診察時的治療率

感 染 來 源	治 療 率	
	ZYVOX 600mg 每 12 小時一次 n/N (%)	ZYVOX 200mg 每 12 小時一次 n/N (%)
任何部位	39/58 (67)	24/46 (52)
任何部位且併發相關的菌血症	10/17 (59)	4/14 (29)
不知來源的菌血症	5/10 (50)	2/7 (29)
皮膚和皮膚組織	9/13 (69)	5/5 (100)
泌尿道	12/19 (63)	12/20 (60)
肺炎	2/3 (67)	0/1 (0)
其他*	11/13 (85)	5/13 (39)

* 感染來源如: 肝膿瘍、膽道膿血症、壞死的膽囊、結腸周圍膿瘍、膿瘍和導管相關的感染。

14.2 兒童病人

革蘭氏陽性菌造成的感染

一項安全性和有效性研究提供了兒童病人以 ZYVOX 治療院內肺炎、複雜性皮膚及皮膚組織感染、和其他由革蘭氏陽性病原菌造成的感染,包括對 methicillin 有抗藥性的 *Staphylococcus aureus*、對 methicillin 有感受性的 *Staphylococcus aureus*、對 vancomycin 有抗藥性 *Enterococcus faecium*。證實或疑似有革蘭氏陽性菌時的感染的出生到 11 歲兒童病人被選為一隨機、開放性對照試驗的受試者。其中一組接受 ZYVOX 10mg/kg 靜脈注射、每 12 小時一次,隨後接受 ZYVOX 口服懸浮劑 10mg/kg、每 8 小時一次;另一組接受 vancomycin 10 至 15mg/kg 靜脈注射、每 6 至 24 小時一次,視年齡與腎臟廓清率而定。證實有 VRE 感染的病人被歸在第三組,接受 ZYVOX 10mg/kg 靜脈注射及/或口服、每 8 小時一次。所有的病人都接受總共 10 至 28 天的治療,如果临床上需要,可以併用對抗革蘭氏陰性菌的抗生素。這個意圖治療(ITT)研究群體有 206 名病人隨機接受 linezolid 治療,102 名病人隨機接受 vancomycin 治療。表十八為 ITT、MITT、及临床上可評估的受試者中之治療率。於研究完成後,又納入一個年齡介於 4 天至 16 歲、13 名病人的開放性延伸試驗 VRE 組。

表十八列出從微生物學上可評估的受試者中 (包括由延伸試驗中,以微生物學評估具

30

ZYVOX 製劑的儲存

儲存於 25°C 以下應避光。瓶口應緊閉以避免潮濕。

16. 病人資訊

應勸告病人,抗菌劑(包括 ZYVOX)只可用來治療細菌感染,它們對病毒感染無效(如感冒)。當處方 ZYVOX 治療細菌感染時,應該告訴病人,雖然在治療早期就會覺得比較好了,仍應完全遵照指示服藥。漏服劑量或不完成整個療程會導致(1)立即性療效會降低,以及(2)細菌產生抗藥性的可能性增加,將來 ZYVOX 或其他抗菌劑對其會無效。

應告知病人:

- ZYVOX 可與食物或空服時服用。
- 如果病人有高血壓的病史,應告知醫師。
- 服用 ZYVOX 時,應該避免食用含大量酪胺(tyramine)的食物或飲料。高 tyramine 含量的食物包括藉由久存、發酵、醃漬或煙乾以增加味道的方法所產生的變性蛋白質;例如:陳年乳酪;發酵或風乾的肉類;醃泡菜;醬油;桶裝啤酒;及紅酒。如果儲存的時間過久或不正確的冷藏,任何高蛋白食物中的 tyramine 含量可能會增加。
- 如果服用含有 pseudoephedrine HCl 或 phenylpropanolamine HCl 的藥品如感冒藥或去鼻塞的藥物時,應該告訴醫師。
- 如果服用血清素回收(serotonin re-uptake)抑制劑或其他抗憂鬱劑時,應該告訴醫師。
- 苯酮尿症(Phenylketonurics): 每 5 毫升 100mg/5mL 的 ZYVOX 口服懸浮劑含 20 毫克的苯丙胺酸(phenylalanine)。其他 ZYVOX 製劑不含苯丙胺酸。詢問您的醫師及藥師。
- 如果視力改變,應告知醫師。
- 如果病人有痙攣的病史,應告知醫師。
- 腹瀉是使用抗生素的一個常見問題,通常在抗生素停用後會消失。有時在開始抗生素治療後,病人會發生水便及血(伴有或沒有胃腸脹及發燒),甚至在服用抗生素最後一個劑量後兩三個月時出現。若發生此種現象,應立即告知醫師。
- 告知病人,特別是以 linezolid 治療時可能發生低血糖反應(如發汗及衰弱)及低血糖測量值之糖尿病病人。要是發生這類反應,病人應聯繫醫生或其他醫護專業人員以獲得妥善治療。

版本: USPI 204802-201807-2

製造廠:

31

32

Pfizer Pharmaceuticals LLC

KM. 1.9 Road 689, Vega Baja, Puerto Rico 00693

銷商：輝瑞大藥廠股份有限公司

地址：[台北市信義區松仁路 100 號 42、43 樓](#) [新北市淡水區中正東路二段 177 號](#)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX formulations and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

1. INDICATIONS AND USAGE

ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION and CLINICAL STUDIES). Linezolid 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).

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia (see CLINICAL STUDIES).

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

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

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

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2. DOSAGE AND ADMINISTRATION

The recommended dosage for ZYVOX formulations for the treatment of infections is described in Table 1

Table 1. Dosage Guidelines for ZYVOX

Infection*	Dosage, Route and Frequency of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Complicated skin and skin structure infections Community-acquired pneumonia, including concurrent bacteremia Nosocomial pneumonia	10 mg/kg IV or oral [†] q8h	600 mg IV or oral [†] q12h	10 to 14
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg IV or oral [†] q8h	600 mg IV or oral [†] q12h	14 to 28
Uncomplicated skin and skin structure infections	less than 5 yrs: 10 mg/kg oral [†] q8h 5-11 yrs: 10 mg/kg oral [†] q12h	Adults: 400 mg oral [†] q12h Adolescents: 600 mg oral [†] q12h	10 to 14

* Due to the designated pathogens [see INDICATIONS AND USAGE (1)]

† Neonates less than 7 days: Most pre-term neonates less than 7 days of age (gestational age less than 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life [see USE IN SPECIFIC POPULATIONS, Pediatric Use (8.4), CLINICAL PHARMACOLOGY (12.3)]

† Oral dosing using either ZYVOX Tablets or ZYVOX for Oral Suspension.

Adult patients with infection due to MRSA should be treated with ZYVOX 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 to oral administration. Patients whose therapy is started with ZYVOX I.V. Injection may be switched to either ZYVOX Tablets or Oral Suspension at the discretion of the physician, when clinically indicated.

3. DOSAGE FORMS AND STRENGTHS

ZYVOX Tablets are available as follows:

600 mg (white, capsule-shaped, film-coated tablets printed with "ZYVOX 600 mg")

4. CONTRAINDICATIONS

4.1 Hypersensitivity

ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

4.2 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.

5. WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

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 pre-treatment 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.

5.2 Peripheral and Optic Neuropathy

Peripheral and optic neuropathies have been reported in patients treated with ZYVOX, primarily in 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. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days. Peripheral and optic neuropathy has also been reported in children.

If patients experience symptoms of visual impairment, 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 ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX. If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks.

5.3 Serotonin Syndrome

Spontaneous reports of serotonin syndrome including fatal cases associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported.

Unless clinically appropriate and patients are carefully observed for signs and/or symptoms of serotonin syndrome or neuroleptic malignant syndrome-like (NMS-like) reactions, 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, bupropion, or buspirone [see DRUG INTERACTIONS (7) and CLINICAL PHARMACOLOGY (12.3)].

In some cases, a patient already receiving a serotonergic antidepressant or buspirone may require urgent treatment with linezolid. If alternatives to linezolid are not available and the potential benefits of linezolid outweigh the risks of serotonin syndrome or NMS-like reactions, the serotonergic antidepressant should be stopped promptly and linezolid administered. The patient should be monitored for two weeks (five weeks if fluoxetine was taken) or until 24 hours after the last dose of linezolid, whichever comes first. Symptoms of serotonin syndrome or NMS-like reactions include hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that include extreme agitation (progressing to delirium and coma). The patient should also be monitored for discontinuation symptoms of the antidepressant (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).

5.4 Mortality Imbalance in an Investigational Study in Patients with Catheter-related Bloodstream Infections, including those with Catheter-site Infections

An imbalance in 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%); odds ratio 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, but was not seen in patients with Gram-positive infections only.

Linezolid is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

Linezolid has no clinical activity against Gram-negative pathogens and 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 INDICATIONS AND USAGE (1)]

5.5 *Clostridium difficile* Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ZYVOX, 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.

5.6 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), vasopressor agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine) [see DRUG INTERACTIONS (7) and CLINICAL PHARMACOLOGY (12.3)]

5.7 Lactic Acidosis

Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation.

5.8 Convulsions

Convulsions have been reported in patients when treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported.

5.9 Hypoglycemia

Post-marketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid, a reversible, non-selective MAO inhibitor. Some MAO inhibitors have been associated with hypoglycemic episodes in diabetic patients receiving insulin or hypoglycemic agents. While a causal relationship between linezolid and hypoglycemia has not been established, diabetic patients should be cautioned of potential hypoglycemic reactions when treated with linezolid.

If hypoglycemia occurs, a decrease in the dose of insulin or oral hypoglycemic agent, or discontinuation of oral hypoglycemic agent, insulin, or linezolid may be required.

5.10 Development of Drug-resistant Bacteria

Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days.

Of the patients treated for uncomplicated skin and skin structure infections (uSSSIs), 25.4% of ZYVOX treated and 19.6% of comparator-treated patients experienced at least one drug-related adverse event. For all other indications, 20.4% of ZYVOX-treated and 14.3% of comparator-treated patients experienced at least one drug-related adverse event.

Table 2 shows the incidence of all-causality, treatment-emergent adverse reactions reported in at least 1% of adult patients in these trials by dose of ZYVOX.

Table 2. Incidence (%) of Treatment-emergent Adverse Reactions Occurring in ≥1% of Adult Patients Treated with ZYVOX in Comparator-controlled Clinical Trials

Adverse Reactions	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg PO q12h (n=548)	Clarithromycin 250 mg PO q12h (n=537)	ZYVOX 600 mg q12h (n=1498)	All Other Comparators* (n=1464)
Headache	8.8	8.4	5.7	4.4
Diarrhea	8.2	6.1	8.3	6.4
Nausea	5.1	4.5	6.6	4.6
Vomiting	2.0	1.5	4.3	2.3
Dizziness	2.6	3.0	1.8	1.5
Rash	1.1	1.1	2.3	2.6
Anemia	0.4	0	2.1	1.4
Taste alteration	1.8	2.0	1.0	0.3
Vaginal moniliasis	1.8	1.3	1.1	0.5
Oral moniliasis	0.5	0	1.7	1.0
Abnormal liver function tests	0.4	0.2	1.6	0.8
Fungal infection	1.5	0.2	0.3	0.2
Tongue discoloration	1.3	0	0.3	0
Localized abdominal pain	1.3	0.6	1.2	0.8
Generalized abdominal pain	0.9	0.4	1.2	1.0

* Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Of the patients treated for uSSSIs, 3.5% 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 2.1% of ZYVOX-treated and 1.7% of comparator-treated patients. The most common reported drug-related adverse events leading to discontinuation of treatment were nausea, headache, diarrhea, and vomiting.

Pediatric Patients

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

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

* Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

† Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, 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.

Laboratory Abnormalities

ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult 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 ZYVOX and 1.5% (range among studies: 0.4% to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, 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 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX 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 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined [see WARNINGS AND PRECAUTIONS (5.1)].

Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The incidence of adult and pediatric patients with at least one substantially abnormal hematologic or serum chemistry value is presented in Tables 4, 5, 6, and 7.

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

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg q12h	Clarithromycin 250 mg q12h	ZYVOX 600 mg q12h	All Other Comparators†
Hemoglobin (g/dL)	0.9	0.0	7.1	6.6
Platelet count (x 10 ³ /mm ³)	0.7	0.8	3.0	1.8
WBC (x 10 ³ /mm ³)	0.2	0.6	2.2	1.3
Neutrophils (x 10 ³ /mm ³)	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.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

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

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	ZYVOX 400 mg q12h	Clarithromycin 250 mg q12h	ZYVOX 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 (mg/dL)	0.2	0.0	0.9	1.1
BUN (mg/dL)	0.2	0.0	2.1	1.5
Creatinine (mg/dL)	0.2	0.0	0.2	0.6

¹ 2 x ULN and 2 x baseline for values abnormal at baseline.
² 2 x ULN and 2 x baseline for values abnormal at baseline.
³ Comparators included cefprozil 200 mg PO q12h, ceftriaxone 1 g IV q12h, dicloxacillin 500 mg PO q6h, oxacillin 2 g IV q6h, vancomycin 1 g IV q12h.

Table 6. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal¹ Hematology Laboratory Value in Comparator-controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections ¹		All Other Indications ²	
	ZYVOX	Cefadroxil	ZYVOX	Vancomycin
Hemoglobin (g/dL)	0.0	0.0	15.7	12.4
Platelet count (x 10 ³ /mm ³)	0.0	0.4	12.9	13.4
WBC (x 10 ³ /mm ³)	0.8	0.8	12.4	10.3
Neutrophils (x 10 ³ /mm ³)	1.2	0.8	5.9	4.3

¹ 75% (-50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline.
² 75% (-50% for neutrophils) of LLN and 75% (-50% for neutrophils, -90% for hemoglobin if baseline LLN) of baseline for values abnormal at baseline.
³ Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h.
⁴ Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.
⁵ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Table 7. Percent of Pediatric Patients who Experienced at Least One Substantially Abnormal¹ Serum Chemistry Laboratory Value in Comparator-controlled Clinical Trials with ZYVOX

Laboratory Assay	Uncomplicated Skin and Skin Structure Infections ¹		All Other Indications ²	
	ZYVOX	Cefadroxil	ZYVOX	Vancomycin
ALT (U/L)	0.0	0.0	10.1	12.5
Lipase (U/L)	0.4	1.2	—	—
Amylase (U/L)	—	—	0.6	1.3
Total bilirubin (mg/dL)	—	—	6.3	5.2
Creatinine (mg/dL)	0.4	0.0	2.4	1.0

¹ 2 x ULN and 2 x baseline for values abnormal at baseline; 2 x ULN and 2 x baseline for total bilirubin x baseline for values abnormal at baseline.
² Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h.
³ Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.
⁴ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of ZYVOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) [see WARNINGS AND PRECAUTIONS (5.1)]; sideroblastic anemia.

9

ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day.

In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.06-fold the estimated human exposure based on AUCs).

When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on post-natal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in pre-implantation loss.

8.3 Nursing Mothers

Linezolid 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 ZYVOX is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years [see INDICATIONS AND USAGE (1), CLINICAL PHARMACOLOGY (12.3) and CLINICAL STUDIES (14)]:

- nosocomial pneumonia;
- complicated skin and skin structure infections;
- community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years);
- vancomycin-resistant *Enterococcus faecium* infections.

The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years [see CLINICAL STUDIES (14)]:

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

Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended.

The pharmacokinetics of linezolid have been evaluated in pediatric patients from birth to 17 years of age. In general, weight-based clearance of linezolid gradually decreases with increasing age of pediatric patients. However, in preterm (gestational age <34 weeks) neonates <7 days of age, linezolid clearance is often lower than in full-term

- Peripheral neuropathy and optic neuropathy sometimes progressing to loss of vision [see WARNINGS AND PRECAUTIONS (5.2)].
- Lactic acidosis [see WARNINGS AND PRECAUTIONS (5.7)]. Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy.
- Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX [see WARNINGS AND PRECAUTIONS (5.3)].
- Convulsions [see WARNINGS AND PRECAUTIONS (5.8)].
- Anaphylaxis, angioedema, and bullous skin disorders including severe cutaneous adverse reactions (SCAR) such as toxic epidermal necrolysis and Stevens-Johnson syndrome.
- Superficial tooth discoloration and tongue discoloration have been reported with the use of linezolid. The tooth discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome.
- Hypoglycemia, including symptomatic episodes [see WARNINGS AND PRECAUTIONS (5.9)].

7. DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase. [see CONTRAINDICATIONS (4.2) and CLINICAL PHARMACOLOGY (12.3)]

7.2 Adrenergic and Serotonergic Agents

Linezolid has the potential for interaction with adrenergic and serotonergic agents. [see WARNINGS AND PRECAUTIONS (5.3, 5.6) and CLINICAL PHARMACOLOGY (12.3)].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects - Pregnancy Category C

Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.06-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see Non-teratogenic Effects). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects

In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased post-implantation embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion.

In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced

10

neonates <7 days of age. Consequently, preterm neonates <7 days of age may need an alternative linezolid dosing regimen of 10 mg/kg every 12 hours [see DOSAGE AND ADMINISTRATION (2.1) and CLINICAL PHARMACOLOGY (12.3)].

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with minimum inhibitory concentrations (MICs) of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response [see CLINICAL PHARMACOLOGY (12.3) and DOSAGE AND ADMINISTRATION (2)].

8.5 Geriatric Use

Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

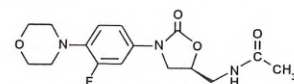
10. OVERDOSAGE

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 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid 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.

11. DESCRIPTION

ZYVOX Tablets contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide.

The empirical formula is C₁₆H₂₀FN₃O₄. Its molecular weight is 337.35, and its chemical structure is represented below:



ZYVOX Tablets for oral administration contain 400 mg or 600 mg linezolid as film-coated compressed tablets. Inactive ingredients are Corn starch, Microcrystalline cellulose, Hydroxypropyl cellulose, Purified water, Sodium starch glycolate, Carnauba wax, Isopropyl alcohol, Magnesium stearate, Opacode red S-1-15118, Opadry white YS-1-18202-A. The sodium (Na⁺) content is 1.95 mg per 400-mg tablet and 2.92 mg per

600-mg tablet (0.1 mEq per tablet, regardless of strength).

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZYVOX is an antibacterial drug [(see MICROBIOLOGY (12.4)).

12.2 Pharmacodynamics

In a randomized, positive- and placebo-controlled crossover thorough QT study, 40 healthy subjects were administered a single ZYVOX 600 mg dose via a 1-hour IV infusion, a single ZYVOX 1200 mg dose via a 1-hour IV infusion, placebo, and a single oral dose of positive control. At both the 600 mg and 1200 mg ZYVOX doses, no significant effect on QTc interval was detected at peak plasma concentration or at any other time.

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of linezolid in adults after single and multiple oral and intravenous doses are summarized in Table 8. Plasma concentrations of linezolid at steady-state after oral doses of 600 mg given every 12 hours (q12h) are shown in Figure 1.

Table 8. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	C _{max} µg/mL	C _{min} µg/mL	T _{max} hrs	AUC ^a µg·h/mL	t _{1/2} hrs	CL mL/min
600 mg tablet						
single dose	12.70 (3.96)	—	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
every 12 hours	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg IV injection^b						
single dose	12.90 (1.60)	—	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
every 12 hours	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)
600 mg oral suspension						
single dose	11.00 (2.76)	—	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)

^a AUC for single dose = AUC_{0-∞}; for multiple-dose = AUC_{0-12h}.

^b Data dose-normalized from 625 mg IV dose was given as 0.5-hour infusion.

C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; T_{max} = Time to C_{max}; AUC = Area under concentration-time curve; t_{1/2} = Elimination half-life; CL = Systemic clearance

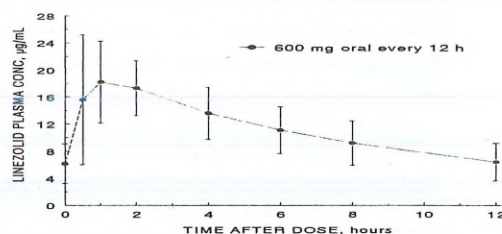


Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-state Following Oral Dosing Every 12 Hours (Mean ± Standard Deviation, n=16)

Absorption: Linezolid is extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, linezolid may be given orally or intravenously without dose adjustment.

Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as AUC_{0-∞} values is similar under both conditions.

Distribution: Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well-perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent. The volume of distribution of linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase I volunteer studies following multiple dosing of linezolid. The ratio of linezolid in saliva relative to plasma was 1.2 to 1 and the ratio of linezolid in sweat relative to plasma was 0.55 to 1.

Metabolism: Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid metabolite (A), and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a non-enzymatic chemical oxidation mechanism *in vitro*. *In vitro* studies have demonstrated that linezolid is minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of linezolid is not fully understood.

Excretion: Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as linezolid, 40% as metabolite B, and 10% as metabolite A. The mean renal

clearance of linezolid is 40 mL/min) which suggests net tubular reabsorption. Virtually no linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B, and 3% as metabolite A.

A small degree of non-linearity in clearance was observed with increasing doses of linezolid, which appears to be due to lower renal and non-renal clearance of linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

Specific Populations

Geriatric Patients: The pharmacokinetics of linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

Pediatric Patients: The pharmacokinetics of linezolid following a single intravenous dose were investigated in pediatric patients ranging in age from birth through 17 years (including premature and full-term neonates), in healthy adolescent subjects ranging in age from 12 through 17 years, and in pediatric patients ranging in age from 1 week through 12 years. The pharmacokinetic parameters of linezolid are summarized in Table 9 for the pediatric populations studied and healthy adult subjects after administration of single IV doses.

The C_{max} and the volume of distribution (V_d) of linezolid are similar regardless of age in pediatric patients. However, plasma clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, weight-based clearance is most rapid in the youngest age groups ranging from <1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As the age of pediatric patients increases, the weight-based clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population. There is increased inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg every 8 hours. Pediatric patients 12 years and older should receive 600 mg every 12 hours [see DOSAGE AND ADMINISTRATION (2)].

Table 9. Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single Intravenous Infusion of 10 mg/kg or 600 mg Linezolid (Mean: (%CV); [Min, Max Values])

Age Group	C _{max} µg/mL	V _d L/kg	AUC ^a µg·h/mL	t _{1/2} hrs	CL mL/min/kg
Neonatal Patients					
Pre-term ^b <1 week (N=9) ^c	12.7 (30%) [9.6, 22.2]	0.81 (24%) [0.43, 1.05]	108 (47%) [41, 191]	5.6 (46%) [2.4, 9.8]	2.0 (52%) [0.9, 4.0]
Full-term ^b <1 week (N=10) ^c	11.5 (24%) [8.0, 18.3]	0.78 (20%) [0.45, 0.96]	55 (47%) [19, 103]	3.0 (55%) [1.3, 6.1]	3.8 (55%) [1.5, 8.8]
Full-term ^b ≥1 week to ≤28 days (N=10) ^c	12.9 (28%) [7.7, 21.6]	0.66 (29%) [0.35, 1.06]	34 (21%) [23, 50]	1.5 (17%) [1.2, 1.9]	5.1 (22%) [3.3, 7.2]

Infant Patients >28 days to <1 months (N=12) ^c	11.0 (27%) [7.2, 18.0]	0.79 (26%) [0.42, 1.08]	33 (26%) [17, 48]	1.8 (28%) [1.2, 2.8]	5.4 (32%) [3.5, 9.9]
Pediatric Patients 3 months through 11 years ^b (N=59)	15.1 (30%) [6.8, 36.7]	0.69 (28%) [0.31, 1.50]	58 (54%) [19, 153]	2.9 (53%) [0.9, 8.0]	3.8 (53%) [1.0, 8.5]
Adolescent Subjects and Patients 12 through 17 years ^b (N=36)	16.7 (24%) [9.9, 28.9]	0.61 (15%) [0.44, 0.79]	95 (44%) [32, 178]	4.1 (46%) [1.3, 8.1]	2.1 (53%) [0.9, 5.2]
Adult Subjects ^d (N=29)	12.5 (21%) [8.2, 19.3]	0.65 (16%) [0.45, 0.84]	91 (33%) [53, 155]	4.9 (35%) [1.8, 8.3]	1.7 (34%) [0.9, 3.3]

^a AUC = Single-dose AUC_{0-∞}.

^b In this data set, "pre-term" is defined as <34 weeks gestational age (Note: Only 1 patient enrolled was pre-term with a post-natal age between 1 week and 28 days).

^c In this data set, "full-term" is defined as ≥34 weeks gestational age.

^d Dose of 10 mg/kg

^e Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg.

^f Dose normalized to 600 mg

C_{max} = Maximum plasma concentration; V_d = Volume of distribution; AUC = Area under concentration-time curve; t_{1/2} = Apparent elimination half-life; CL = Systemic clearance normalized for body weight.

Gender: Females have a slightly lower volume of distribution of linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. After a 600-mg dose, mean oral clearance is approximately 38% lower in females than in males. However, there are no significant gender differences in mean apparent elimination-rate constant or half-life. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

Renal Impairment: The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal impairment; however, the two primary metabolites of linezolid accumulate in patients with renal impairment, with the amount of accumulation increasing with the severity of renal dysfunction (see Table 10). The pharmacokinetics of linezolid and its two metabolites have also been studied in patients with end-stage renal disease (ESRD) receiving hemodialysis. In the ESRD study, 14 patients were dosed with linezolid 600 mg every 12 hours for 14.5 days (see Table 11). Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal impairment. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal impairment should be weighed against the potential risks of accumulation of these metabolites. Both linezolid and the two metabolites are eliminated by hemodialysis. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Approximately 30% of a dose was eliminated in a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after hemodialysis.

Table 10. Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Patients with Varying Degrees of Renal Impairment after a Single 600-mg Oral Dose of Linezolid

Parameter	Healthy Subjects CL _{CR} > 80 mL/min	Moderate Renal Impairment 30 < CL _{CR} < 80 mL/min	Severe Renal Impairment 10 < CL _{CR} < 30 mL/min
Linezolid			
AUC ₀₋₂₄ , µg h/mL	110 (22)	128 (53)	127 (66)
t _{1/2} , hours	6.4 (2.2)	6.1 (1.7)	7.1 (3.7)
Metabolite A			
AUC ₀₋₂₄ , µg h/mL	7.6 (1.9)	11.7 (4.3)	56.5 (30.6)
t _{1/2} , hours	6.3 (2.1)	6.6 (2.3)	9.0 (4.6)
Metabolite B¹			
AUC ₀₋₂₄ , µg h/mL	30.5 (6.2)	51.1 (38.5)	203 (92)
t _{1/2} , hours	6.6 (2.7)	9.9 (7.4)	11.0 (3.9)

¹ Metabolite B is the major metabolite of linezolid.

Table 11. Mean (Standard Deviation) AUCs and Elimination Half-lives of Linezolid and Metabolites A and B in Subjects with End-Stage Renal Disease (ESRD) after the Administration of 600 mg Linezolid Every 12 Hours for 14.5 Days

Parameter	LINEZOLID	ESRD Subjects ¹
AUC ₀₋₁₂ , µg h/mL (after last dose)		181 (52.3)
t _{1/2} , h (after last dose)		8.3 (2.4)
METABOLITE A		
AUC ₀₋₁₂ , µg h/mL (after last dose)		153 (40.6)
t _{1/2} , h (after last dose)		15.9 (8.5)
METABOLITE B²		
AUC ₀₋₁₂ , µg h/mL (after last dose)		356 (99.7)
t _{1/2} , h (after last dose)		34.8 (23.1)

¹ Between hemodialysis sessions

² Metabolite B is the major metabolite of linezolid

Hepatic Impairment: The pharmacokinetics of linezolid are not altered in patients (n=7) with mild-to-moderate hepatic impairment (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for patients with mild-to-moderate hepatic impairment. The pharmacokinetics of linezolid in patients with severe hepatic impairment have not been evaluated

Drug Interactions

Drugs Metabolized by Cytochrome P450

Linezolid is not an inducer of cytochrome P450 (CYP450) in rats. In addition, linezolid does not inhibit the activities of clinically significant human CYP isoforms (e.g., 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, linezolid is not expected to affect the pharmacokinetics of other drugs metabolized by these major enzymes. 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.

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.

Antioxidants

The potential for drug-drug interactions with linezolid and the antioxidants Vitamin C and Vitamin E was studied in healthy volunteers. Subjects were administered a 600 mg oral dose of linezolid on Day 1, and another 600 mg dose of linezolid on Day 8. On Days 2-9, subjects were given either Vitamin C (1000 mg/day) or Vitamin E (800 IU/day). The AUC₀₋₂₄ of linezolid increased 2.3% when co-administered with Vitamin C and 10.9% when co-administered with Vitamin E. No linezolid dose adjustment is recommended during co-administration with Vitamin C or Vitamin E.

Strong CYP 3A4 Inducers

Rifampin: The effect of rifampin on the pharmacokinetics of linezolid was evaluated in a study of 16 healthy adult males. Volunteers were administered oral linezolid 600 mg twice daily for 5 doses with and without rifampin 600 mg once daily for 8 days. Co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid C_{max} [90% CI, 15%-27%] and a 32% decrease in linezolid AUC₀₋₁₂ [90% CI, 27%-37%]. The clinical significance of this interaction is unknown. The mechanism of this interaction is not fully understood and may be related to the induction of hepatic enzymes. Other strong inducers of hepatic enzymes (e.g., carbamazepine, phenytoin, phenobarbital) could cause a similar or smaller decrease in linezolid exposure.

Monoamine Oxidase Inhibition

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic Agents

Some individuals receiving ZYVOX 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.

Tyramine: A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content [see PATIENT COUNSELING INFORMATION (16)].

Pseudoephedrine HCl or phenylpropanolamine HCl: A reversible enhancement of the pressor response to either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects [see WARNINGS AND PRECAUTIONS (5.6), DRUG INTERACTIONS (7)]. 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 every 12 hours 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

17

seen 2 to 3 hours after the second dose of PPA or PSE, and returned to baseline 2 to 3 hours after peak. The results of the PPA study follow, showing the mean (and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg (range: 20-52 mm Hg) and 38 mm Hg (range: 18-79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively.

Serotonergic Agents

Dextromethorphan: 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, hyperreflexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

12.4 Microbiology

Mechanism of Action

Linezolid is a synthetic antibacterial agent of the oxazolidinone class, which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The *in vitro* spectrum of activity of linezolid also includes certain Gram-negative bacteria and anaerobic bacteria. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is essential for bacterial reproduction. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of isolates.

Resistance

In vitro studies have shown that point mutations in the 23S rRNA are associated with linezolid resistance. Reports of vancomycin-resistant *Enterococcus faecium* becoming resistant to linezolid during its clinical use have been published. There are reports of *Staphylococcus aureus* (methicillin-resistant) developing resistance to linezolid during clinical use. The linezolid resistance in these organisms is associated with a point mutation in the 23S rRNA (substitution of thymine for guanine at position 2576) of the organism. Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to linezolid. Also linezolid resistance in staphylococci mediated by the enzyme methyltransferase has been reported. This resistance is mediated by the *cfr* (chloramphenicol-florfenicol) gene located on a plasmid which is transferable between staphylococci.

Interaction with Other Antimicrobial Drugs

In vitro studies have demonstrated additivity or indifference between linezolid and vancomycin, gentamicin, rifampin, imipenem-cilastatin, aztreonam, ampicillin, or streptomycin.

Linezolid has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections [see INDICATIONS AND USAGE (1)].

Gram-positive bacteria

Enterococcus faecium (vancomycin-resistant isolates only)
Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

The following *in vitro* data are available, but their clinical significance is unknown. Greater than 90% of the following bacteria exhibit an *in vitro* MIC less than or equal to the linezolid-susceptible breakpoint for organisms of similar genus. The safety and effectiveness of linezolid in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

Enterococcus faecalis (including vancomycin-resistant isolates)
Enterococcus faecium (vancomycin-susceptible isolates)
Staphylococcus epidermidis (including methicillin-resistant isolates)
Staphylococcus haemolyticus
Viridans group streptococci

Gram-negative bacteria

Pasteurella multocida

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of linezolid. Neither mutagenic nor clastogenic potential was found in a battery of tests including: assays for mutagenicity (Ames bacterial reversion and CHO cell mutation), an *in vitro* unscheduled DNA synthesis (UDS) assay, an *in vitro* chromosome aberration assay in human lymphocytes, and an *in vivo* mouse micronucleus assay.

Linezolid did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ≥50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). The reversible fertility effects were mediated through altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. Epithelial cell hypertrophy and hyperplasia in the epididymis was observed in conjunction with decreased fertility. Similar epididymal changes were not seen in dogs.

19

20

In sexually mature male rats exposed to drug as juveniles, mildly decreased fertility was observed following treatment with linezolid through most of their period of sexual development (50 mg/kg/day from days 7 to 36 of age, and 100 mg/kg/day from days 37 to 55 of age), with exposures up to 1.7-fold greater than mean AUCs observed in pediatric patients aged 3 months to 11 years. Decreased fertility was not observed with shorter treatment periods, corresponding to exposure *in utero* through the early neonatal period (gestation day 6 through post-natal day 5), neonatal exposure (post-natal days 5 to 21), or to juvenile exposure (post-natal days 22 to 35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats treated from post-natal day 22 to 35.

13.2 Animal Toxicology and/or Pharmacology

Target organs of linezolid toxicity were similar in juvenile and adult rats and dogs. Dose- and time-dependent myelosuppression, as evidenced by bone marrow hypocellularity/decreased hematopoiesis, decreased extramedullary hematopoiesis in spleen and liver, and decreased levels of circulating erythrocytes, leukocytes, and platelets have been seen in animal studies. Lymphoid depletion occurred in thymus, lymph nodes, and spleen. Generally, the lymphoid findings were associated with anorexia, weight loss, and suppression of body weight gain, which may have contributed to the observed effects.

In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was evident in 2 male rats after 6 months of dosing, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The nerve degeneration observed was microscopically comparable to spontaneous unilateral optic nerve degeneration reported in aging rats and may be an exacerbation of common background change.

These effects were observed at exposure levels that are comparable to those observed in some human subjects. The hematopoietic and lymphoid effects were reversible, although in some studies, reversal was incomplete within the duration of the recovery period.

14. CLINICAL STUDIES

14.1 Adults

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a randomized, multi-center, double-blind trial. Patients were treated for 7 to 21 days. One group received ZYVOX I.V. Injection 600 mg q12h, and the other group received vancomycin 1 g q12h IV. Both groups received concomitant aztreonam (1 to 2 g every 8 hours IV), which could be continued if clinically indicated. There were 203 linezolid-treated and 193 vancomycin-treated patients enrolled in the study. One hundred twenty-two (60%) linezolid-treated patients and 103 (53%) vancomycin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 57% for linezolid-treated patients and 60% for vancomycin-treated patients. The cure

rates in clinically evaluable patients with ventilator-associated pneumonia were 47% for linezolid-treated patients and 40% for vancomycin-treated patients. A modified intent-to-treat (MITT) analysis of 94 linezolid-treated patients and 83 vancomycin-treated patients included subjects who had a pathogen isolated before treatment. The cure rates in the MITT analysis were 57% in linezolid-treated patients and 46% in vancomycin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 12.

Table 12. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Nosocomial Pneumonia

Pathogen	Cured	
	ZYVOX n/N (%)	Vancomycin n/N (%)
<i>Staphylococcus aureus</i>	23/38 (61)	14/23 (61)
Methicillin-resistant <i>S. aureus</i>	13/22 (59)	7/10 (70)
<i>Streptococcus pneumoniae</i>	9/9 (100)	9/10 (90)

Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections were enrolled in a randomized, multi-center, double-blind, double-dummy trial comparing study medications administered IV followed by medications given orally for a total of 10 to 21 days of treatment. One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX Tablets 600 mg q12h; the other group received oxacillin 2 g every 6 hours (q6h) IV followed by dicloxacillin 500 mg q6h orally. Patients could receive concomitant aztreonam if clinically indicated. There were 400 linezolid-treated and 419 oxacillin-treated patients enrolled in the study. Two hundred forty-five (61%) linezolid-treated patients and 242 (58%) oxacillin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 90% in linezolid-treated patients and 85% in oxacillin-treated patients. A modified intent-to-treat (MITT) analysis of 316 linezolid-treated patients and 313 oxacillin-treated patients included subjects who met all criteria for study entry. The cure rates in the MITT analysis were 86% in linezolid-treated patients and 82% in oxacillin-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 13.

Table 13. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Complicated Skin and Skin Structure Infections

Pathogen	Cured	
	ZYVOX n/N (%)	Oxacillin/Dicloxacillin n/N (%)
<i>Staphylococcus aureus</i>	73/83 (88)	72/84 (86)
Methicillin-resistant <i>S. aureus</i>	2/3 (67)	0/0 (-)
<i>S. aureus</i>	6/6 (100)	3/6 (50)
<i>Streptococcus agalactiae</i>	12/17 (71)	2/3 (67)
<i>Streptococcus pyogenes</i>	18/26 (69)	21/28 (75)

Table 14. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Adult Patients with Diabetic Foot Infections

Pathogen	Cured	
	ZYVOX n/N (%)	Comparator n/N (%)
<i>Staphylococcus aureus</i>	49/63 (78)	20/29 (69)
Methicillin-resistant <i>S. aureus</i>	12/17 (71)	2/3 (67)
<i>Streptococcus agalactiae</i>	25/29 (86)	9/16 (56)

Vancomycin-Resistant Enterococcal Infections

Adult patients with documented or suspected vancomycin-resistant enterococcal infection were enrolled in a randomized, multi-center, double-blind trial comparing a high dose of ZYVOX (600 mg) with a low dose of ZYVOX (200 mg) given every 12 hours (q12h) either intravenously (IV) or orally for 7 to 28 days. Patients could receive concomitant aztreonam or aminoglycosides. There were 79 patients randomized to high-dose linezolid and 66 to low-dose linezolid. The intent-to-treat (ITT) population with documented vancomycin-resistant enterococcal infection at baseline consisted of 65 patients in the high-dose arm and 52 in the low-dose arm.

The cure rates for the ITT population with documented vancomycin-resistant enterococcal infection at baseline are presented in Table 15 by source of infection. These cure rates do not include patients with missing or indeterminate outcomes. The cure rate was higher in the high-dose arm than in the low-dose arm, although the difference was not statistically significant at the 0.05 level.

Table 15. Cure Rates at the Test-of-Cure Visit for ITT Adult Patients with Documented Vancomycin-Resistant Enterococcal Infections at Baseline

Source of Infection	Cured	
	ZYVOX 600 mg q12h n/N (%)	ZYVOX 200 mg q12h n/N (%)
Any site	39/58 (67)	24/46 (52)
Any site with associated bacteremia	10/17 (59)	4/14 (29)
Bacteremia of unknown origin	5/10 (50)	2/7 (29)
Skin and skin structure	9/13 (69)	5/5 (100)
Urinary tract	12/19 (63)	12/20 (60)
Pneumonia	2/3 (67)	0/1 (0)
Other*	11/13 (85)	5/13 (39)

* Includes sources of infection such as hepatic abscess, biliary sepsis, necrotic gall bladder, pericolic abscess, pancreatitis, and catheter-related infection.

14.2 Pediatric Patients

Infections Due to Gram-positive Bacteria

A safety and efficacy study provided experience on the use of ZYVOX in pediatric patients for the treatment of nosocomial pneumonia, complicated skin and skin structure infections, and other infections due to Gram-positive bacterial pathogens, including methicillin-resistant and -susceptible *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Pediatric patients ranging in age from birth through 11 years with infections caused by the documented or suspected Gram-positive bacteria were enrolled in a randomized, open-label, comparator-controlled trial. One group of patients received ZYVOX I.V. Injection 10 mg/kg every 8 hours (q8h) followed by ZYVOX for Oral Suspension 10 mg/kg q8h. A second group received vancomycin 10 to 15 mg/kg

A separate study provided additional experience with the use of ZYVOX in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. This was a randomized, open-label trial in hospitalized adult patients with documented or suspected MRSA infection.

One group of patients received ZYVOX I.V. Injection 600 mg q12h followed by ZYVOX Tablets 600 mg q12h. The other group of patients received vancomycin 1 g q12h IV. Both groups were treated for 7 to 28 days, and could receive concomitant aztreonam or gentamicin if clinically indicated. The cure rates in microbiologically evaluable patients with MRSA skin and skin structure infection were 26/33 (79%) for linezolid-treated patients and 24/33 (73%) for vancomycin-treated patients.

Diabetic Foot Infections

Adult diabetic patients with clinically documented complicated skin and skin structure infections ("diabetic foot infections") were enrolled in a randomized (2:1 ratio), multi-center, open-label trial comparing study medications administered IV or orally for a total of 14 to 28 days of treatment. One group of patients received ZYVOX 600 mg q12h IV or orally; the other group received ampicillin/sulbactam 1.5 to 3 g IV or amoxicillin/clavulanate 500 to 875 mg every 8 to 12 hours (q8-12h) orally. In countries where ampicillin/sulbactam is not marketed, amoxicillin/clavulanate 500 mg to 2 g every 6 hours (q6h) was used for the intravenous regimen. Patients in the comparator group could also be treated with vancomycin 1 g q12h IV if MRSA was isolated from the foot infection. Patients in either treatment group who had Gram-negative bacilli isolated from the infection site could also receive aztreonam 1 to 2 g q8-12h IV. All patients were eligible to receive appropriate adjunctive treatment methods, such as debridement and off-loading, as typically required in the treatment of diabetic foot infections, and most patients received these treatments. There were 241 linezolid-treated and 120 comparator-treated patients in the intent-to-treat (ITT) study population. Two hundred twelve (86%) linezolid-treated patients and 105 (88%) comparator-treated patients were clinically evaluable. In the ITT population, the cure rates were 68.5% (165/241) in linezolid-treated patients and 64% (77/120) in comparator-treated patients, where those with indeterminate and missing outcomes were considered failures. The cure rates in the clinically evaluable patients (excluding those with indeterminate and missing outcomes) were 83% (159/192) and 73% (74/101) in the linezolid- and comparator-treated patients, respectively. A critical post-hoc analysis focused on 121 linezolid-treated and 60 comparator-treated patients who had a Gram-positive pathogen isolated from the site of infection or from blood, who had less evidence of underlying osteomyelitis than the overall study population, and who did not receive prohibited antimicrobials. Based upon that analysis, the cure rates were 71% (86/121) in the linezolid-treated patients and 63% (38/60) in the comparator-treated patients. None of the above analyses were adjusted for the use of adjunctive therapies. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 14.

IV every 6 to 24 hours, depending on age and renal clearance. Patients who had confirmed VRE infections were placed in a third arm of the study and received ZYVOX 10 mg/kg q8h IV and/or orally. All patients were treated for a total of 10 to 28 days and could receive concomitant Gram-negative antibiotics if clinically indicated. In the intent-to-treat (ITT) population, there were 206 patients randomized to linezolid and 102 patients randomized to vancomycin. The cure rates for ITT, MITT, and clinically evaluable patients are presented in Table 16. After the study was completed, 13 additional patients ranging from 4 days through 16 years of age were enrolled in an open-label extension of the VRE arm of the study. Table 17 provides clinical cure rates by pathogen for microbiologically evaluable patients including microbiologically evaluable patients with vancomycin-resistant *Enterococcus faecium* from the extension of this study.

Table 16. Cure Rates at the Test-of-Cure Visit for Intent to Treat, Modified Intent to Treat, and Clinically Evaluable Pediatric Patients for the Overall Population and by Select Baseline Diagnosis

Population	ITT		MITT		Clinically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)	ZYVOX n/N (%)	Vancomycin n/N (%)
Any diagnosis	150/186 (81)	69/83 (83)	86/108 (80)	44/49 (90)	106/117 (91)	49/54 (91)
Complicated skin and skin structure infections	61/72 (85)	31/34 (91)	37/43 (86)	22/23 (96)	46/49 (94)	26/27 (96)
Nosocomial pneumonia	13/18 (72)	11/12 (92)	5/6 (83)	4/4 (100)	7/7 (100)	5/5 (100)

MITT = ITT patients with an isolated Gram-positive pathogen at baseline

Table 17. Cure Rates at the Test-of-Cure Visit for Microbiologically Evaluable Pediatric Patients with Infections due to Gram-positive Pathogens

Pathogen	Microbiologically Evaluable	
	ZYVOX n/N (%)	Vancomycin n/N (%)
Vancomycin-resistant <i>Enterococcus faecium</i>	6/8 (75)*	0/0 (-)
<i>Staphylococcus aureus</i>	36/38 (95)	23/24 (96)
Methicillin-resistant <i>S. aureus</i>	16/17 (94)	9/9 (100)
<i>Streptococcus pyogenes</i>	2/2 (100)	1/2 (50)

*Includes data from 7 patients enrolled in the open-label extension of this study

15. HOW SUPPLIED

Tablets

ZYVOX Tablets are available as follows:

600 mg (white, capsule-shaped, film-coated tablets printed with "ZYVOX 600 mg")
100 tablets in HDPE bottle
20 tablets in HDPE bottle
Unit dose packages of 30 tablets

Storage of ZYVOX Formulations

Store at 25°C (77°F). Protect from light. Keep bottles tightly closed to protect from moisture.

16. PATIENT COUNSELING INFORMATION

Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future.

Patients should be advised that:

- ZYVOX may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses, fermented or air-dried meats, sauerkraut, soy sauce, tap beers, and red wines. The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.
- They should inform their physician if taking medications containing pseudoephedrine HCl or phenyl propanolamine HCl, such as cold remedies and decongestants.
- They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants.
- Phenylketonurics:** Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist.
- They should inform their physician if they experience changes in vision.
- They should inform their physician if they have a history of seizures.
- Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.
- Inform patient, particularly those with diabetes mellitus that hypoglycemic reactions, such as diaphoresis and tremulousness, along with low blood glucose measurements may occur when treated with linezolid. If such reactions occur, patients should contact a physician or other health professional for proper treatment.

Manufacture site:

Pfizer Pharmaceuticals LLC
KM 1.9 Road 689, Vega Baja, Puerto Rico 00693.

Pharmaceutical company: Pfizer Limited
42, 43F., No. 100, Songren Road, Xinyi District, Taipei City, Taiwan.

Version: USPI 201807-2

正本

檔 號：

保存年限：

衛生福利部 函

機關地址：11558 台北市南港區忠孝東路六段488號

傳 真：

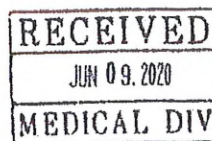
聯絡人及電話：詹美玲02-27877481

電子郵件信箱：mlchan@fda.gov.tw

110

台北市信義區松仁路100號42,43樓

受文者：輝瑞大藥廠股份有限公司



發文日期：中華民國109年6月4日

發文字號：衛授食字第1096015532號

速別：普通件

密等及解密條件或保密期限：

附件：仿單核定本1份。

主旨：有關貴公司申請藥品許可證「采福適膜衣錠」(衛署藥輸字第023181號)原料藥廠廠名及仿單變更一案(案號：1096015532)，本部同意，隨函檢還仿單核定本1份，請查照。

說明：

- 一、復貴公司109年5月20日109輝瑞法規字第202017號函及108年9月11日108輝瑞法規字第192046號藥品變更登記申請書。
- 二、核准變更項目：
 - (一)原料藥製造廠名變更為「Pfizer Asia Manufacturing Pte Ltd」。
 - (二)仿單變更。
- 三、有關仿單規定如下：市售藥品得僅放置經審查核定之中文仿單。但如市售藥品同時放置中、外文仿單者，外文仿單內容須與核定本之中文仿單內容相符，廠商得依核定之中文仿單自行修正其外文仿單內容。
- 四、自109年7月1日起，藥品許可證之「展延案」、「自請註銷案」及「藥品上市後行政變更案」將採全面「藥品查驗登記審查暨線上申請作業平台」線上送件申請，紙本送件概不予受理。

正本：輝瑞大藥廠股份有限公司

副本：

部長陳時中