威洛速® 靜脈輸注液400公絲/250公撮
AVELOX® Infusion Solution 400mg/250ml

主成分: moxifloxacin hydrochloride　抗生素　靜脈輸注液　衛署藥輸字第023712號

組成

每袋/瓶250公撮無菌輸注液含有436公絲的moxifloxacin hydrochloride，相當於400公絲的moxifloxacin。

藥理性質

Moxifloxacin是一種廣效且具有殺菌作用的fluoroquinolone類抗生素。在活體外試驗中，moxifloxacin具有廣泛的抗菌範圍，如革蘭氏陽性菌，革蘭氏陰性菌，厭氧菌，acid-fast bacteria，以及一些非典型的菌種，例如 *Mycoplasma spp.*，*Chlamydia spp.*與*Legionella spp.*。

Moxifloxacin用於對β-lactam及macrolide有抗藥性的菌種依然有效。而在動物的感染試驗中，moxifloxacin展現了高度的活體活性。

不論是活體外試驗或臨床上的感染，moxifloxacin對於以下所列的大部分菌種，均有抗菌活性。

革蘭氏陽性菌

Staphylococcus aureus（包括對methicillin敏感的菌種）
Streptococcus pneumoniae（包括對penicillin和macrolide產生抗藥性的菌種）
Streptococcus pyogenes (group A)

革蘭氏陰性菌

Haemophilus influenzae（包括會產生及不會產生β-lactamase的菌種）
Haemophlius parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis（包括會產生及不會產生β-lactamase的菌種）
Escherichia coli
Enterobacter cloacae

非典型菌種

Chlamydia pneumoniae
Mycoplasma pneumoniae
Legionella pneumophila

根據活體外試驗的結果，下列的菌種對moxifloxacin具有敏感性。然而，臨床上使用moxifloxacin治療由這些微生物所引起感染的安全和有效性，尚未確立。

革蘭氏陽性菌

Streptococcus milleri
Streptococcus mitior
Streptococcus agalatiae
Streptococcus dysgalactiae
Staphylococcus cohnii
Staphylococcus epidermidis（包括對methicillin敏感的菌種）
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus saprophyticus
Staphylococcus simulans
Corynebacterium diphtheriae

革蘭氏陰性菌

Bordetella pertussis
Klebsiella oxytoca
Enterobacter aerogenes
Enterobacter agglomerans
Morganella morganii
Providencia stuartii
Enterobacter intermedius
Enterobacter sakazaki
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri

厭氧菌

Bacteroides distasonis
Bacteroides eggerthii
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Fusobacterium spp
Porphyromonas spp
Porphyromonas anaerobius
Porphyromonas asaccharolyticus
Porphyromonas magnus
Prevotella spp
Propionibacterium spp
Clostridium perfringens
Clostridium ramosum

非典型菌種

Coxiella burnettii

Moxifloxacin的殺菌作用來自於它會對topoisomerase II和IV產生干擾。而topoisomerases是一群控制DNA的形成(topology)和協助DNA的複製、修復與轉錄的必要酵素。

Moxifloxacin的殺菌效果取決於它的濃度。一般而言，它的最低殺菌濃度與它的最低抑菌濃度相近。

會使penicillins，cephalosporins，aminoglycosides，macrolides和tetracyclines失效的抗藥性機轉，並不會干擾moxifloxacin的抗菌活性，所以moxifloxacin與這些藥品並不會產生交叉抗藥性。到目前為止，尚未發現由質體傳遞的抗藥性。總體而言，抗藥性發生的頻率相當低(10^{-7}-10^{-10})。在活體外試驗中發現，moxifloxacin的抗藥性經由數個步驟的突變緩慢形成。

即使微生物連續暴露在moxifloxacin低於最低抑菌濃度的環境下，moxifloxacin的最低抑菌濃度仍只有些許的增加。Quinolones類的藥物彼此間已知有交叉抗藥性。然而，已對其他的quinolones類的藥物產生抗藥性的一些革蘭氏陽性菌及厭氧菌種仍對moxifloxacin有敏感。

由酵素CYP3A4, CYP2D6, CYP2C9, CYP2C19或CYP1A2代謝的藥物的代謝清除。如同其他的quinolone類，鐵(Iron)及制酸劑(Antacid)則明顯地降低moxifloxacin的生體可用率。

Itraconazole: 在一個有11位健康自願受試者的臨床試驗中，cytochrome P450 3A4的強效抑制劑 - Itraconazole（每天200公絲持續9天），其對moxifloxacin的藥物動力學並無明顯的影響（在itraconazole給藥第7天給予一劑400公絲的moxifloxacin）。另外，moxifloxacin也顯示對itraconazole的藥物動力學沒有影響。

Theophylline: 在一個有12位健康自願受試者的臨床試驗中，moxifloxacin（每12小時200公絲持續3天）對theophylline（每12小時400公絲持續3天）的藥物動力學並無明顯的影響。另外，theophylline並未顯示對moxifloxacin的藥物動力學有影響。尚未研究併服400公絲的moxifloxacin和theophylline的作用，但基於體外試驗的代謝資料顯示moxifloxacin沒有抑制CYP1A2酵素，臨床上應無明顯的作用。

Warfarin: 在一個有24位健康自願受試者的臨床試驗中，moxifloxacin（每天400公絲持續8天）對R-及S-warfarin（在第5天時給予單一劑量warfarin sodium 25公絲）的藥物動力學並無明顯的影響，且對凝血　原時間亦無明顯改變。已有報告指出包括moxifloxain在內的quinolone類藥物會加強病患warfarin或其衍生物的抗凝血劑作用。而病患所感染的疾病及其所伴隨的發炎過程、年齡和一般情況都是抗凝血活性增加的危險因子。因此，當quinolone與warfarin或其衍生物併用時，必須謹慎地監測凝血　原時間、INR(International Normalized Ratio)或其他合適的凝血功能測試。

Digoxin: 在一個有12位健康自願受試者的臨床試驗中，moxifloxacin（每天400公絲持續2天）對digoxin（單一劑量0.6公絲）的AUC並無明顯的影響。在digoxin 分佈期，其平均C_{max}增加了約50%。這digoxin C_{max}短暫增加的現象在臨床上的影響並不明顯。不管是否有digoxin存在，moxifloxacin的藥物動力學都是相似的。當併用moxifloxacin和digoxin時，不需要調整兩者之劑量。

嗎啡(morphine)：在一個有20位健康男性和女性自願受試者的臨床試驗中，morphine sulfate（單一劑量10公絲肌肉注射）對moxifloxacin（單一劑量400公絲）的平均AUC及C_{max}無明顯的影響。

口服避孕劑(oral contraceptives)：在一個以安慰劑作對照組、29位健康女性受試者的臨床試驗中，每天400公絲的moxifloxacin持續7天不會干擾0.15公絲levonorgestrel/0.03公絲ethinylestradiol的口服避孕劑的內分泌抑制作用（經由血清測得progesterone, FSH, estradiol和LH），或是干擾口服避孕劑的藥物動力學。

Probenecid: 在一個有12位健康自願受試者的臨床試驗中，probenecid（500公絲每天2次持續2天）不會改變moxifloxacin（單一劑量400公絲）腎清除及經由腎排除的總量。

Ranitidine: 在一個有10位健康自願受試者的臨床試驗中，ranitidine（治療前以150公絲每天2次持續3天）對moxifloxacin（單一劑量400公絲）的藥物動力學無明顯的影響。

Antidiabetic agents: 與安慰劑比較，服用moxifloxacin（每天400公絲持續5天）的糖尿病患，其glyburide（治療前每天2.5公絲持續2個星期後再同時併用5天）的平均AUC及C_{max}相對於低12%和21%。但是，比起只服用glyburide，同時服用glyburide和moxifloxacin的病患其血糖有輕微的下降。暗示glyburide的活性不會受moxifloxacin干擾，這樣交互作用的結果並不視為有臨床上的意義。

鈣(calcium)：12位健康自願受試者同時服用moxifloxacin（單一劑量400公絲）及鈣（單一劑量500公絲鈣離子營養補充劑），接著在moxifloxacin服用後12及24小時各追加一劑鈣，鈣對moxifloxacin的平均AUC沒有明顯的影響。Moxifloxacin與鈣同時服用，與單獨服用moxifloxacin相比，平均C_{max}有輕微的降低，而其達到血中最高濃度所需的時間延長了（2.5小時相對於0.9小時），這些差異並不視為有臨床上的意義。

心電圖(Electrocardiogram)：已有觀察到部份服用moxifloxacin的病患其心電圖的QT間隔時間延長。口服400公絲moxifloxacin，在藥物最大濃度時其QTc與服用前時比較，其變化的平均值（及其標準差）為6毫秒(± 26) (n = 787)。在每天靜脈輸注療程中（400公絲，每天輸注一小時），與第一天治療前相比，第一天的平均QTc變化為9毫秒(± 24) (n = 69)，而第3天為3毫秒(± 29) (n = 290)。

Moxifloxacin與其他會延長心電圖QTc間隔的藥物間，在人體藥物藥效上交互作用的相關資料有限。當併用Sotalol（Class III抗心律不整藥物）和靜脈輸注高劑量moxifloxacin於狗時，顯示QTc間隔時間有增加的情形。因此，moxifloxacin必須避免與Class IA和Class III抗心律不整藥物使用。（參見" 警語及注意事項"）

適應症

用於治療成人（18歲以上）感受性細菌引起的感染症，包括：上呼吸道及下呼吸道感染（急性鼻竇炎、慢性支氣管炎的急性惡化、社區性肺炎），皮膚和軟組織的感染。

使用禁忌

已知對本輸注液的任何組成成分或其他的quinolones過敏者。

Avelox輸注液禁止使用於小孩、正在成長中的青少年及孕婦。已知quinolones類的藥物會分泌至哺乳婦女的乳汁中。而臨床前的證據指出，仍有少量的moxifloxacin會分泌於人類的乳汁當中。由於尚無哺乳婦女的使用資料，因此moxifloxacin仍禁止使用於孕婦和哺乳婦女。

警語及注意事項

服用quinolones時可能會有癲癇的情況發生。所以moxifloxacin若使用在已知或懷疑有中樞神經疾病的病人，因其可能會導致癲癇或會降低癲癇閾值，必須多加小心。

臨床藥理學

吸收

口服的moxifloxacin錠劑，經由胃腸道的吸收良好。Moxifloxacin的絕對生體可用率約為90%。同時服用高脂肪食物（脂肪提供500卡熱量）也不會影響moxifloxacin的吸收。

Moxifloxacin與一杯優格同時服用不會顯著地影響全身吸收(AUC)的程度或速度。單次及多次劑量口服400公絲moxifloxacin後其最高濃度(C_{max})及血中濃度曲線下面積(AUC)的平均值（及其標準差）摘要如下。

	最高濃度 C_{max}(mg/L)	血中濃度曲線下面積AUC (mg•h/L)	半衰期 Half-life(hr)
口服單次劑量			
健康者 (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
口服多次劑量			
健康青年男性/女性 (n = 15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ± 1.9
健康老年男性 (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
健康老年女性 (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
健康青年男性 (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
健康青年女性 (n = 9)	4.2 ± 0.5	49.3 ± 9.5	

* 平均值的範圍源自不同試驗

單次及多次劑量靜脈輸注400公絲 moxifloxacin一小時的最高濃度(C_{max})及血中濃度曲線下面積(AUC)平均值及其標準差摘要如下。

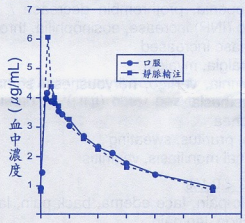
	最高濃度 C_{max}(mg/L)	血中濃度曲線下面積AUC (mg•h/L)	半衰期 Half-life(hr)
靜脈注射單次劑量			
健康青年男性/女性 (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
病患 (n = 118)			
男性 (n = 64)	4.4 ± 3.7		
女性 (n = 54)	4.5 ± 2.0		
< 65歲 (n = 58)	4.6 ± 4.2		
≥ 65歲 (n = 60)	4.3 ± 1.3		
靜脈注射多次劑量			
健康青年男性 (n = 8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
健康老年人 (n =12; 8位男性, 4位女性)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
病患** (n = 107)			
男性 (n = 58)	4.2 ± 2.6		
女性 (n = 49)	4.6 ± 1.5		
< 65歲 (n = 52)	4.1 ± 1.4		
≥ 65歲 (n = 55)	4.7 ± 2.7		

* 平均值的範圍源自不同試驗

** 預期之最高血中濃度（輸注完畢時之濃度）

血漿濃度隨著劑量增加而成比例增加（最高測試劑量為單次口服1200公絲）。血漿排除半衰期的平均值(及其標準差)為12 ± 1.3小時；每天一次400公絲的療法，至少三天後血中濃度可達穩定狀態(steady-state)。

一天一次口服(n=10)或靜脈輸注(n=12)400公絲 moxifloxacin後，穩定狀態時的平均血中濃度



分佈

Moxifloxacin大約有50%與血漿蛋白結合，結合程度不受藥物濃度影響。

Moxifloxacin的分佈體積範圍為1.7-2.7 L/kg。Moxifloxacin 的分佈可遍及全身，組織濃度通常高於血漿濃度。口服或靜脈給予400公絲moxifloxacin後，可在唾液、鼻及支氣管分泌物、鼻竇黏膜、皮膚水泡內的液體、皮下組織及骨骼肌內測得moxifloxacin。給藥後3小時所測得的濃度摘要如下表格所示。Moxifloxacin的組織排除速率通常與血漿排除速率類似。

口服400公絲moxifloxacin後3小時於血漿及組織中所測得的moxifloxacin濃度（平均值及標準差）§

組織或體液	個數 (N)	血漿濃度 (μg/mL)	組織或體液濃度 (μg/mL or μg/g)	組織血漿比例：
呼吸道				
肺泡巨噬細胞	5	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
支氣管黏膜	8	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
上皮內襯液體	5	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
鼻竇				
上頷鼻竇黏膜	4	3.7 ± 1.1†	7.6 ± 1.7	2.0 ± 0.3
前篩骨黏膜	3	3.7 ± 1.1†	8.8 ± 4.3	2.2 ± 0.6
鼻息肉	4	3.7 ± 1.1†	9.8 ± 4.5	2.6 ± 0.6

§ 所有moxifloxacin濃度皆為單次給予400公絲劑量後測得，只有鼻竇(sinus)的濃度是給藥五天後測得

† N = 5

由於臨床資料有限，不建議moxifloxacin使用於肝功能嚴重受損（Child Pugh C）的病人。

如同其他的一些quinolones和macrolides的藥物，moxifloxacin會延長某些病患心電圖的QT間隔時間。QT間隔時間延長的病患、未矯正的低鉀血症病患、服用class IA（例如：quinidine, procainamide）或class III（例如：amiodarone, sotalol）之抗心律不整藥物病患，應避免服用 moxifloxacin，因為尚缺乏這些病患服用moxifloxacin的臨床經驗。

不可排除moxifloxacin和延長QT間隔時間藥物（例如：cisapride, erythromycin, antipsychotics, tricyclic antidepressants）的加成作用，因此，moxifloxacin與這些藥物併用時須特別注意。

Moxifloxacin用於心律不整前期的病患須特別注意，例如臨床上明顯心跳過慢或急性心肌缺血。

QT延長作用的強度可能會隨著moxifloxacin濃度增加而增加，因此，不可超過建議劑量及60分鐘內輸注400公絲的速率。QT間隔時間延長可能會增加心室心律不整的危險性（包括torsades de pointes）。超過8000位以口服及注射moxifloxacin治療的病患並未有歸因於QTc間隔時間延長而造成心血管方面的發病或死亡，然而，特定的易發狀況可能會增加心室心律不整的危險性。

Quinolone（包括moxifloxacin）治療可能發生韌帶發炎及斷裂，特別是老年人和同時服用皮質類固醇的病人。如果開始有疼痛或發炎的症狀，必須停止藥物治療並且讓受影響的四肢休息。

曾有報告指出，使用廣效性抗生素（包括moxifloxacin）會有偽膜性結腸炎發生，所以服用moxifloxacin的病人若有嚴重腹瀉的情形，需考慮是否為此一病症，在此種臨床情況下，須立即給予病人適當的治療及評估。

光敏感(Photosensitivity)：使用其他的quinolone類藥物時，曾有光敏感性的報告。然而，根據以人類為自願者的研究中指出，moxifloxacin並無測出有光毒性的可能。雖然如此，必須告訴病人要避免紫外線或陽光過度照射。

有些個案，病人在第一次服用後即有過敏反應，醫生應立即被告知。

某些情況下，第一次服用後，有極少數的過敏反應案例會演變成致命性的休克，在這情況下，必須停止使用moxifloxacin並採取醫療措施（例如治療休克）。

不良反應

在moxifloxacin的臨床試驗中，大多數的不良藥品反應為輕微到中度（大約90 %）。因不良藥品反應而停藥的病人，在口服給藥的試驗中，其比例為3.6 %，而在靜脈輸注後接著口服的試驗中，其比例為5.7 %。根據moxifloxacin所有的臨床試驗研究，最常見的不良藥品反應（其關聯性定義為很有可能、有可能、無法評估）如下所列：

發生頻率≧1%且<10%

全身性	*腹痛、頭痛、注射處反應（例如：水腫/過敏/發炎/疼痛）*
心血管系統	*併有低鉀血症病患的QT間隔時間延長*
消化系統	*噁心、腹瀉、嘔吐、消化不良、肝功能測試異常*
特殊感覺	*味覺倒置*
神經系統	*眩暈*

發生頻率≧0.1%且<1%

全身性	*無力衰弱、念珠菌病、疼痛、不適、胸痛*
心血管系統	*心搏過速、高血壓、心悸、QT間隔時間延長、靜脈炎（輸注部位）*
消化系統	*嘴乾、噁心、嘔吐、脹氣、便秘、口腔念珠菌病、食慾不振、口腔炎、胃腸道不適、舌炎、γ GT 增加*
血液及淋巴系統	*白血球減少、凝血酵素原下降 / International Normalized Ration (INR)增加、嗜伊紅血球過多、血小板增多症*
代謝及營養	*澱粉酵素增加*
骨骼肌肉系統	*關節痛、肌肉痛*
神經系統	*失眠、眩暈、緊張、嗜睡、焦慮、發抖、感覺倒置*
呼吸系統	*呼吸困難*
皮膚及附屬部位	*紅疹、搔癢、流汗*
生殖泌尿系統	*陰道念珠菌病、陰道炎*

發生頻率≧0.01%且<0.1%

全身性	*下腹痛、面部水腫、背痛、生化檢驗值異常、過敏反應、腳痛*
心血管系統	*低血壓、血管舒張、週邊水腫*
消化系統	*胃炎、舌頭變色、吞嚥困難、黃疸（顯著地膽汁鬱滯）、腹瀉 (Clostridium difficile)*
血液及淋巴系統	*凝血酵素下降、凝血酵素原增加 / International Normalized Ration (INR) 下降、血小板減少、貧血*
代謝及營養	*血糖過高、血脂肪過高、尿酸過高、低密度脂蛋白增加 (與肝功能異常有關)*
骨骼肌肉系統	*關節炎、韌帶不適*
神經系統	*幻覺、人格解體、壓力過大、不協調、興奮、健忘、失語症、情緒不穩、睡眠失調、說話能力失調、思考不正常、感覺遲鈍、不正常的夢境、痙攣、困惑、沮喪*
呼吸系統	*氣喘*
皮膚及附屬部位	*紅疹（斑丘疹、紫斑病、膿包）、蕁麻疹*
特殊感覺	*耳鳴、視覺異常、喪失味覺、嗅覺異常（包括嗅覺倒錯、嗅覺減弱及喪失）、弱視*
生殖泌尿系統	*腎功能異常（肌酐酸或尿素增加）*

上市後調查報告中的不良反應：

發生頻率≧0.01%且<0.1%

心血管系統	*暈厥*

發生頻率< 0.01%

過敏性	*過敏反應、休克（過敏性的、可能有致命危險）、血管水腫（包括喉水腫、潛在有致命危險）*
消化系統	*偽膜性結腸炎（極少數案例中與有致命危險的併發症有關）、肝炎（顯著地膽汁鬱滯）*
骨骼肌肉系統	*肌腱斷裂*
皮膚及附屬部位	*Stevens-Johnson Syndrome*
神經系統	*精神方面的反應*
心血管系統	*極少數案例，尤其是嚴重潛在的心律不整前期的病患，通報有心室心律不整（包括torsade de pointes及心跳停止）的情形。（見"警語及注意事項"）*

代謝
口服或靜脈輸注單一劑量moxifloxacin，約52% moxifloxacin是經由與glucuronide和sulfate結合而代謝。Cytochrome P450系統與moxifloxacin的代謝無關，也不會被moxifloxacin影響。大約38%的劑量會變成sulfate結合物(M1)，且主要由糞便中排除。大約14%的口服或靜脈注射劑量會轉變成glucuronide結合物(M2)，完全由尿液排除。M2的最高血漿濃度約為原藥的40%，而M1的血中濃度通常都小於moxifloxacin血中濃度的10%。
Cytochrome (CYP) P450酵素的體外試驗顯示出moxifloxacin不會抑制CYP3A4、CYP2D6、CYP2C9、CYP2C19或CYP1A2，這表示moxifloxacin不會改變經由這些酵素代謝的藥物的藥物動力學。

排泄
大約45%的口服或靜脈注射moxifloxacin是以原型藥排泄（尿中約20%而糞便中約25%）。全部口服劑量的96% ± 4%會以原型藥或已知的代謝物排出。全身清除率及腎清除率的平均值（及其標準差）分別為12 ± 2.0 L/hr及2.6 ± 0.5 L/hr。

特殊族群
年老病患：
分別給16位老年人（8位男性；8位女性）及17位青年人（8位男性；9位女性）健康自願受試者口服400公絲的moxifloxacin，連續服用十天後發現，在moxifloxacin的藥物動力學上並沒有與年齡相關的改變。給予16位健康男性自願受試者（8位青年人；8位老年人）單次口服200公絲的moxifloxacin，發現全身吸收藥物的程度（AUC和C_{max}）在青年男性及老年男性間沒有統計上的差異，且排除半衰期沒有改變。因此不需要因年齡不同而作劑量的調整。在大型的第三期臨床試驗中，老年病患靜脈注射400公絲moxifloxacin完畢時的濃度，與青年病患相似。
小兒族群：
並未有小兒族群使用moxifloxacin藥物動力學的研究。
性別：
分別給23位健康男性（19到75歲）及24位健康女性（19到70歲）口服400公絲的moxifloxacin十天後發現，女性AUC及最高濃度C_{max}的平均值較男性分別高8%及16%。即使考慮男性與女性的體重不同，moxifloxacin在男性及女性的藥物動力學上並沒有顯著差異。
已進行一個包含18位青年男性及女性單次使用400公絲moxifloxacin比較藥物動力學的研究。在這研究中（9位青年男性及9位青年女性）顯示，AUC或C_{max}並沒有因性別而不同。所以基於性別不同而作劑量調整是不需要的。
種族：
日本男性及白種人其moxifloxacin穩定狀態時的藥物動力學相似，一天口服400公絲後，其平均C_{max}為4.1 μg/mL，AUC_{24}為47 μg•h/mL，排除半衰期為14小時
腎功能不全：
輕微、中度、嚴重或末期腎臟疾病並不會明顯改變moxifloxacin藥物動力學參數，腎功能損傷的病患，包括需要血液透析(HD)和攜帶式連續腹膜透析(CAPD)的病人，都不須調整劑量。
在一個有24位不同腎功能程度（從正常到嚴重損傷）病患口服單一劑量的研究中，中度腎功能損傷(30 mL/min ≤ CL_{CR} ≤ 60 mL/min)及嚴重腎功能損傷(CL_{CR} < 30 mL/min)的病患，其平均moxifloxacin最高濃度(C_{max})分別降低了21%及28%，而這些病患的平均AUC則增加了13%。中度及嚴重腎功能損傷的病患，其sulfate結合物(M1)的平均AUC增加了1.7倍（最大到2.8倍），而glucuronide結合物(M2)的平均AUC及C_{max}分別增加了2.8倍（最大到4.8倍）及1.4倍（最大到2.5倍）。
針對血液透析或攜帶式連續腹膜透析的病人（CL_{CR} < 20 mL/min）進行了單一劑量及多次劑量moxifloxacin的藥物動力學研究（8 HD, 8 CAPD）。在口服單一劑量400公絲後，與一般健康自願受試者相比，HD和CAPD病患其moxifloxacin的AUC並無明顯不同；與健康自然控制者相比，HD和CAPD病患其moxifloxacin的C_{max}值則分別下降約45%和33%。這些病患的sulfate結合物(M1)其AUC增加了1.4到1.5倍。相對於健康受試者，其glucuronide結合物(M2)的平均AUC增加了7.5倍而平均C_{max}則增加了2.5到3倍。Moxifloxacin的sulfate及glucuronide結合物在微生物學上並無活性，這些包括HD和CAPD的腎病變患者其代謝物增加在臨床上的意義尚未研究。HD或CAPD病患每天一次口服400公絲moxifloxacin連續七天，其moxifloxacin的平均AUCss與健康受試者的相似。HD病患其穩定狀態的C_{max}值比健康受試者約低22%，但CAPD病患則與健康受試者相當。HD和CAPD病患皆只移除體內少許的moxifloxacin（HD約9%而CAPD約3%）。HD和CAPD亦分別移除4%和2%的glucuronide代謝物(M2)。
肝功能不全：
在一個有6位輕微肝功能不全（Child Pugh Class A）及10位中度肝功能不全（Child Pugh Class B）的病患口服單一劑量400公絲的研究中，moxifloxacin平均AUC分別是18位健康控制組的78%及102%，而平均最高濃度C_{max}是控制組的79%及84%。輕微及中度這兩組，其moxifloxacin的sulfate結合物(M1)其平均AUC分別增加了3.9倍（最大到5.9倍）和5.7倍（最大到8.0倍），而兩組M1的平均C_{max}都增加了約3倍（最大到4.7和3.9倍）。Moxifloxacin的glucuronide結合物(M2) 其平均AUC兩組都增加了1.5倍（最大到2.5倍），M2的平均Cmax分別增加了1.6及1.3倍（最大到2.7和2.1倍）。Sulfate和glucuronide結合物的增加在臨床上的意義尚未研究。建議輕微及中度肝功能不全(Child Pugh Classes A and B)的病患不須作劑量調整。嚴重肝功能不全 (Child Pugh Class C) 病患的moxifloxacin藥物動力學尚未研究。（參見"**用法用量**"）

光敏感可能性
在一個有32位健康自願受試者（每組8位）針對紫外線（UVA和UVB）及可見光對皮膚反應的研究顯示，與安慰劑比較，moxifloxacin並未有光毒性。分別以moxifloxacin（每天200公絲或400公絲）、lomefloxaicn（每天400公絲）及安慰劑治療，在治療前後測量最小紅斑劑量(Minimum Erythematous Dose, MED)。在這項研究中，兩種劑量的moxifloxacin所測得的MED並沒有顯著不同於安慰劑組，但lomefloxacin的MED明顯地較低。（參見"**警語及注意事項**"）

藥物交互作用
Moxifloxacin與itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, oral contraceptives, ranitidine, glyburide和calcium間潛在的藥物動力學上的交互作用已經被評估。臨床上moxifloxacin對itraconazole, theophylline, warfarin, digoxin, oral contraceptives, glyburide的動力學並無明顯的影響。Itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, ranitidine及 calcium並無明顯影響moxifloxacin的藥物動力學。由體外試驗得到的數據及結果推測， moxifloxacin不太可能明顯地改變經

其他與藥物無關且未列於上述不良藥物反應中的生化檢驗參數改變，最常見的有：血比容的增加或減少、白血球上升、紅血球上升或下降、血糖降低、血紅素降低、alkaline phosphatase 增加、SGOT/AST上升、SGPT/ALT上升、膽紅素增加、尿素增加、肌酐酸增加、BUN上升。

這些生化值的異常是由於藥物或者是因其症狀所致尚未確知。

藥物過量
藥物過量的資料仍有限。對於健康者，一次劑量大至1200公絲以及連續給予十天600公絲的劑量，均尚未發現有明顯的不良效應。若發生過量的情形，建議視病人臨床上的狀況給予適當的支持療法。

在口服moxifloxacin後，在吸收前期用活性碳，可有效預防過量的moxifloxacin。若是經由靜脈給藥，活性炭只能輕微降低（約20%）全身性的吸收，因此在靜脈輸注過量時使用活性碳效果有限。

用法用量《本藥限由醫師使用》
劑量範圍(成人)
Moxifloxacin的建議劑量是一天400公絲。

治療期
治療期的長短必須取決於疾病的嚴重程度或臨床反應。以下是一般治療上呼吸道及下呼吸道感染的建議治療期：
慢性支氣管炎的急性惡化 - 5天。
社區型肺炎 - 建議接續治療（先靜脈輸注而後口服）的總療程為7至14天。
急性鼻竇炎 - 7天。
建議治療皮膚和軟組織感染的療程為7天。

臨床上指出，可以一開始是靜脈輸注，接著改以口服錠劑治療。
在臨床試驗中，輸注 Avelox 曾使用到14天的治療期。

投與方式
此輸注液應靜脈輸注達60分鐘。
本品可直接輸注或與其他相容的輸注液一同輸注。
在室溫下，下列溶液與本品以1:10, 1:1和10:1的比例混合可形成穩定的混合液達24小時，可與之配伍。
- 注射用水 (Water for Injections)
- 0.9 %氯化鈉溶液 (Sodium Chloride 0.9 %)
- 1莫耳氯化鈉溶液 (Sodium Chloride 1 molar)
- 5 %葡萄糖溶液 (Glucose 5 %)
- 10 %葡萄糖溶液 (Glucose 10 %)
- 40 %葡萄糖溶液 (Glucose 40 %)
- 20 %木糖醇 (Xylit 20%)
- 林格氏液 (Ringer Solution)
- 乳酸林格氏液 (Lactated Ringer Solution)
- Aminofusin 10 % (製造廠: Pharmacia & Upjohn)
- Jonosteril D5 (製造廠: Fresenius Kabi)

本品若要與其他藥品併服，必須分開給予。（請見"配伍禁忌"）
只可使用澄清的溶液。

老人
使用於老人不需要調整劑量。

小孩
Moxifloxacin禁止使用於小孩及正在成長中的青少年。（見"使用禁忌"）

肝功能受損的病人
對於肝功能受損的病人，不需要調整劑量，（對Child-Pugh C病人的用法，請見"警語及注意事項"）。

腎功能受損的病人
對於任何程度腎功能受損的病人（包括肌酐酸清除率小於30ml/min/1.73m^2）及長期透析的病人，例如血液透析和攜帶式連續腹膜透析，都不需調整劑量。

種族差異
白人、日本人、黑人及其他種族間可能有種族差異。但臨床上並未見藥物動力學上種族差異，因此，不同種族間不需要調整劑量。

注意事項
配伍禁忌
下列溶液與本品不相容：
- 10 %氯化鈉溶液 (Sodium Chloride 10 %)
- 20 %氯化鈉溶液 (Sodium Chloride 20 %)
- 4.2 %碳酸氫鈉溶液 (Sodium Hydrogen Carbonate 4.2 %)
- 8.4 %碳酸氫鈉溶液 (Sodium Hydrogen Carbonate 8.4 %)

不可冷藏或冷凍。必須存放在原包裝容器中。
貯放在低溫可能會產生沉澱，放在室溫即可再度溶解。因此建議不可將本品貯放在冰箱中。
藥品必須置於兒童無法觸及之處。

包裝
250公撮玻璃瓶及塑膠軟袋裝。

製造廠：Bayer HealthCare AG　德國拜耳藥廠
廠　址：D-51368 Leverkusen, Germany
藥　商：台灣拜耳股份有限公司
地　址：台北市信義路五段7號54樓
電　話：(02)81011000
網　址：www.bayer-pharma.com.tw
AVELOX Infusion Solution 400mg/250ml / OE05_US0604 / TW03 / 092004
01402507/TW/03

AVELOX® Infusion Solution 400mg/250ml

Active substance: moxifloxacin hydrochloride
antibacterial
Infusion solution for intraveneous administration

COMPOSITION

1 single sterile unit polyolefine-bag of 250 ml infusion solution contains 436 mg moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.
1 vial of 250 ml infusion solution contains 436 mg moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.

PROPERTIES

Moxifloxacin is a fluoroquinolone antibacterial with a broad spectrum of activity and bactericidal action. Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative organisms, anaerobes, acid-fast bacteria, and atypicals eg. *Mycoplasma* spp., *Chlamydia* spp. and *Legionella* spp.
Moxifloxacin is effective against ß-lactam and macrolide resistant bacteria. Studies in animal models of infection have demonstrated the high *in vivo* activity.
Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

Gram-positive microorganisms

Staphylococcus aureus (including methicillin-sensitive strains)
Streptococcus pneumoniae (including penicillin and macrolide resistant strains)
Streptococcus pyogenes (group A)

Gram-negative microorganisms

Haemophilus influenzae (including ß-lactamase negative and positive strains)
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis (including ß-lactamase negative and positive strains)
Escherichia coli
Enterobacter cloacae

Atypicals

Chlamydia pneumoniae
Mycoplasma pneumoniae
Legionella pneumophila

According to *in vitro* studies, the following organisms are sensitive to moxifloxacin, however, the safety and effectiveness of moxifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-positive microorganisms

Streptococcus milleri
Streptococcus mitior
Streptococcus agalactiae
Streptococcus dysgalactiae
Staphylococcus cohnii
Staphylococcus epidermidis (including methicillin sensitive strains)
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus saprophyticus
Staphylococcus simulans
Corynebacterium diphtheriae

Gram-negative microorganisms

Bordetella pertussis
Klebsiella oxytoca
Enterobacter aerogenes
Enterobacter agglomerans
Enterobacter intermedius
Enterobacter sakazaki
Proteus mirabilis
Proteus vulgaris
Morganella morganii
Providencia rettgeri
Providencia stuartii

Anaerobes

Bacteroides distasonis
Bacteroides eggerthii
Bacteroides fragilis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides uniformis
Fusobacterium spp
Porphyromonas spp
Porphyromonas anaerobius
Porphyromonas asaccharolyticus
Porphyromonas magnus
Prevotella spp
Propionibacterium spp
Clostridium perfringens
Clostridium ramosum

Atypicals

Coxiella burnetii

The bactericidal action results from the interference with topoisomerase II and IV. Topoisomerases are essential enzymes which control DNA topology and assist in DNA replication, repair and transcription.
Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations.
Resistance mechanisms which inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. There is no cross-resistance between moxifloxacin and these agents. Plasmid-mediated resistance has not been observed to date. A very low overall frequency of resistance was demonstrated (10^{-7} - 10^{-10}). *In vitro* studies have demonstrated that resistance to moxifloxacin develops slowly by multiple step mutations.
Serial exposure of organisms to sub-MIC concentrations of moxifloxacin showed only a small increase in MIC values. Cross-resistance among quinolones has been observed. However, some Gram-positive and anaerobic organisms resistant to other quinolones are susceptible to moxifloxacin.

As with all other quinolones, iron and antacids significantly reduced bioavailability of moxifloxacin.

Itraconazole: In a study involving 11 healthy volunteers, there was no significant effect of itraconazole (200 mg once daily for 9 days), a potent inhibitor of cytochrome P4503A4, on the pharmacokinetics of moxifloxacin (a single 400 mg dose given on the 7th day of itraconazole dosing). In addition, moxifloxacin was shown not to affect the pharmacokinetics of itraconazole.

Theophylline: No significant effect of moxifloxacin (200 mg every twelve hours for 3 days) on the pharmacokinetics of theophylline (400 mg every twelve hours for 3 days) was detected in a study involving 12 healthy volunteers. In addition, theophylline was not shown to affect the pharmacokinetics of moxifloxacin. The effect of co-administration of a 400 mg dose of moxifloxacin with theophylline has not been studied, but it is not expected to be clinically significant based on *in vitro* metabolic data showing that moxifloxacin does not inhibit the CYP1A2 isoenzyme.

Warfarin: No significant effect of moxifloxacin (400 mg once daily for eight days) on the pharmacokinetics of R- and S-warfarin (25 mg single dose of warfarin sodium on the fifth day) was detected in a study involving 24 healthy volunteers. No significant change in prothrombin time was observed. Quinolones, including moxifloxacin, have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are risk factors for increased anticoagulant activity. Therefore the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if a quinolone is administered concomitantly with warfarin or its derivatives.

Digoxin: No significant effect of moxifloxacin (400 mg once daily for two days) on digoxin (0.6 mg as a single dose) AUC was detected in a study involving 12 healthy volunteers. The mean digoxin C_{max} increased by about 50% during the distribution phase of digoxin. This transient increase in digoxin C_{max} is not viewed to be clinically significant. Moxifloxacin pharmacokinetics were similar in the presence or absence of digoxin. No dosage adjustment for moxifloxacin or digoxin is required when these drugs are administered concomitantly.

Morphine: No significant effect of morphine sulfate (a single 10 mg intramuscular dose) on the mean AUC and C_{max} of moxifloxacin (400 mg single dose) was observed in a study of 20 healthy male and female volunteers.

Oral Contraceptives: A placebo-controlled study in 29 healthy female subjects showed that moxifloxacin 400 mg daily for 7 days did not interfere with the hormonal suppression of oral contraception with 0.15 mg levonorgestrel/0.03 mg ethinylestradiol (as measured by serum progesterone, FSH, estradiol, and LH), or with the pharmacokinetics of the administered contraceptive agents.

Probenecid: Probenecid (500 mg twice daily for two days) did not alter the renal clearance and total amount of moxifloxacin (400 mg single dose) excreted renally in a study of 12 healthy volunteers.

Ranitidine: No significant effect of ranitidine (150 mg twice daily for three days as pretreatment) on the pharmacokinetics of moxifloxacin (400 mg single dose) was detected in a study involving 10 healthy volunteers.

Antidiabetic agents: In diabetics, glyburide (2.5 mg once daily for two weeks pretreatment and for five days concurrently) mean AUC and C_{max} were 12% and 21% lower, respectively, when taken with moxifloxacin (400 mg once daily for five days) in comparison to placebo. Nonetheless, blood glucose levels were decreased slightly in patients taking glyburide and moxifloxacin in comparison to those taking glyburide alone, suggesting no interference by moxifloxacin on the activity of glyburide. These interaction results are not viewed as clinically significant.

Calcium: Twelve healthy volunteers were administered concomitant moxifloxacin (single 400 mg dose) and calcium (single dose of 500 mg Ca^{++} dietary supplement) followed by an additional two doses of calcium 12 and 24 hours after moxifloxacin administration. Calcium had no significant effect on the mean AUC of moxifloxacin. The mean C_{max} was slightly reduced and the time to maximum plasma concentration was prolonged when moxifloxacin was given with calcium compared to when moxifloxacin was given alone (2.5 hours versus 0.9 hours). These differences are not considered to be clinically significant.

Electrocardiogram: Prolongation of the QT interval in the ECG has been observed in some patients receiving moxifloxacin. Following oral dosing with 400 mg of moxifloxacin the mean (± SD) change in QTc from the pre-dose value at the time of maximum drug concentration was 6 msec (± 26) (n = 787). Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 msec (± 24) on Day 1 (n = 69) and 3 msec (± 29) on Day 3 (n = 290).

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. Sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with high doses of intravenous (I.V.) moxifloxacin in dogs. Therefore, moxifloxacin should be avoided with Class IA and Class III antiarrhythmics. (See **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**.)

INDICATION

Avelox is indicated for the treatment of adults (≥ 18 years of age) with upper and lower respiratory tract infections such as:

- Acute sinusitis

Absorption

Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The absolute bioavailability of moxifloxacin is approximately 90 percent. Co-administration with a high fat meal (i.e., 500 calories from fat) does not affect the absorption of moxifloxacin. Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally are summarized below.

	C_{max} (mg/L)	AUC (mg·h/L)	Half-life (hr)
Single Dose Oral			
Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ± 1.9
Healthy elderly male (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	

* Range of means from different studies

The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given by 1 hour I.V. infusion are summarized below.

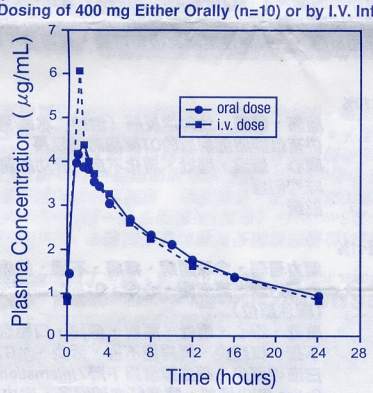
	C_{max} (mg/L)	AUC (mg·h/L)	Half-life (hr)
Single Dose I.V.			
Healthy young male/female (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
Patients (n = 118)			
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2.0		
< 65 years (n = 58)	4.6 ± 4.2		
≥ 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients** (n = 107)			
Male (n = 58)	4.2 ± 2.6		
Female (n = 49)	4.6 ± 1.5		
< 65 years (n = 52)	4.1 ± 1.4		
≥ 65 years (n = 55)	4.7 ± 2.7		

* Range of means from different studies

** Expected C_{max} (concentration obtained around the time of the end of the infusion)

Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained With Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Distribution

Moxifloxacin is approximately 50% bound to serum proteins, independent of drug concentration. The volume of distribution of moxifloxacin ranges from 1.7 to 2.7 L/kg. Moxifloxacin is widely distributed throughout the body, with tissue concentrations often exceeding plasma concentrations. Moxifloxacin has been detected in the saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, and subcutaneous tissue, and skeletal muscle following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarized in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) After Oral Dosing in Plasma and Tissues Measured 3 Hours After Dosing with 400 mg§

Tissue or Fluid	N	Plasma Concentration (mg/mL)	Tissue or Fluid Concentration (mg/mL or mg/g)	Tissue Plasma Ratio:
Respiratory				
Alveolar Macrophages	5	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial Mucosa	8	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial Lining Fluid	5	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus				
Maxillary Sinus Mucosa	4	3.7 ± 1.1†	7.6 ± 1.7	2.0 ± 0.3
Anterior Ethmoid Mucosa	3	3.7 ± 1.1†	8.8 ± 4.3	2.2 ± 0.6
Nasal Polyps	4	3.7 ± 1.1†	9.8 ± 4.5	2.6 ± 0.6

§ all moxifloxacin concentrations were measured after a single 400 mg dose, except the sinus concentrations which were measured after 5 days of dosing.

† N = 5

Metabolism

Approximately 52% of an oral or intravenous dose of moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. The sulfate conjugate (M1) accounts for approximately 38% of the dose, and is eliminated primarily in the feces. Approximately 14% of an oral or intravenous dose is converted to a glucuronide conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

In vitro studies with cytochrome (CYP) P450 enzymes indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

– Community acquired pneumonia

and skin and soft tissue infections.

CONTRA-INDICATIONS

Known hypersensitivity to any component of the infusion solution or other quinolones.

Avelox infusion solution is contraindicated in children, growing adolescents and pregnant women. Quinolones are known to distribute well into breast milk of lactating women. Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. There is no data available in lactating or nursing women. Therefore, the use of moxifloxacin in pregnancy and nursing mothers is contra-indicated.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Seizures may occur with quinolone therapy. Moxifloxacin should be used with caution in patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold.

Due to limited clinical data the use of moxifloxacin is not recommended in patients with severe hepatic impairment (Child Pugh C).

Moxifloxacin, as with some other quinolones and macrolides, has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.

An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded. Therefore, moxifloxacin should be used with caution when given concurrently with these drugs.

Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia.

The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose and infusion rate of 400mg within 60 minutes should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade des pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 8000 patients (oral and parenteral administration), however, certain predisposing conditions may increase the risk for ventricular arrhythmias.

Tendon inflammation and rupture may occur with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue treatment and rest the affected limb(s).

Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics including moxifloxacin; therefore it is important to consider this diagnosis in patients who develop serious diarrhoea in association with the use of moxifloxacin. In this clinical situation adequate therapeutic measures should be initiated immediately.

Photosensitivity: Phototoxicity has been reported with other quinolones. However, a study in human volunteers concluded that moxifloxacin has no measurable phototoxic potential. Nevertheless patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

In some instances, the hypersensitivity and allergic reactions already occurred after the first administration and the doctor should be informed immediately.

Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases moxifloxacin has to be discontinued, medical treatment (e.g. treatment for shock) is required.

UNDESIRABLE EFFECTS

In moxifloxacin clinical trials the majority of adverse drug reactions (ADRs) were described as mild to moderate (approximately 90%). The discontinuation rate of moxifloxacin-treated patients due to ADRs was 3.6% in studies with oral treatment and 5.7% in studies with sequential (intravenous followed by oral) treatment. The most common adverse drug reactions (relationship defined as probable, possible or not assessable) based on all clinical studies with moxifloxacin are listed below:

Incidence of frequency ≥ 1% < 10%

Body as a whole:	abdominal pain, headache, injection site reaction (e.g. edema/ hypersensitivity/inflammation/pain)
Cardiovascular system:	QT prolongation in patients with concomitant hypokalemia
Digestive system:	nausea, diarrhea, vomiting, dyspepsia, abnormal liver function test
Special senses:	taste perversion
Nervous system:	dizziness

Incidence of frequency ≥ 0.1% < 1%

Body as a whole:	asthenia, moniliasis, pain, malaise, chest pain
Cardiovascular system:	tachycardia, hypertension, palpitation, QT prolongation, phlebitis (at infusion site)
Digestive system:	dry mouth, nausea and vomiting, flatulence, constipation, oral moniliasis, anorexia, stomatitis, gastrointestinal disorder, glossitis, γGT increase
Hemic and lymphatic system:	leukopenia, prothrombin decrease / International Normalized Ratio (INR) increase, eosinophilia, thrombocytemia
Metabolic and nutritional:	amylase increased
Musculoskeletal system:	arthralgia, myalgia
Nervous system:	insomnia, vertigo, nervousness, somnolence, anxiety, tremor, paresthesia
Respiratory system:	dyspnea
Skin and appendages:	rash, pruritus, sweating
Urogenital system:	vaginal moniliasis, vaginitis

Incidence of frequency ≥ 0.01% < 0.1%

Body as a whole:	pelvic pain, face edema, back pain, lab test abnormal, allergic reaction, leg pain
Cardiovascular system:	hypotension, vasodilatation, peripheral edema
Digestive system:	gastritis, tongue discoloration, dysphagia, jaundice (predominantly cholestatic), diarrhea (clostridium difficile)
Hemic and lymphatic system:	thromboplastin decrease, prothrombin increase / International Normalized Ratio (INR) decrease, thrombopenia, anemia
Metabolic and nutritional:	hyperglycemia, hyperlipemia, hyperuricemia, LDH increased (in connection with abnormal liver function tests)
Musculoskeletal:	arthritis, tendon disorder
Nervous system:	hallucinations, depersonalization, hypertonia, incoordination, agitation, amnesia, aphasia, emotional lability, sleep disorders, speech disorders, thinking abnormal, hypesthesia, abnormal dreams, convulsion, confusion, depression
Respiratory system:	asthma
Skin and appendages:	rash (maculapapular, purpuric, pustular), urticaria
Special senses:	tinnitus, abnormal vision, taste loss, parosmia (including smell perversion, decreased smell and loss of smell), amblyopia
Urogenital system:	kidney function abnormal (increase in creatinin or urea)

Adverse reactions based on post marketing reports:

Incidence of frequency ≥ 0.01 % < 0.1 %

Cardiovascular:	Syncope

Incidence of frequency < 0.01%

Hypersensitivity:	anaphylactic reaction, shock (anaphylactic, possibly life threatening), angioedema (including laryngeal edema; potentially life-threatening)
Digestive system:	Pseudomembranous colitis (in very rare cases associated with life threatening complications), hepatitis (predominantly

Excretion
Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean (± SD) apparent total body clearance and renal clearance are 12 ± 2.0 L/hr and 2.6 ± 0.5 L/hr, respectively.

Special Populations

Geriatric
Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8 female) and 17 young (8 male; 9 female) healthy volunteers, there were no age-related changes in moxifloxacin pharmacokinetics. In 16 healthy male volunteers (8 young; 8 elderly) given a single 200 mg dose of oral moxifloxacin, the extent of systemic exposure (AUC and C_{max}) was not statistically different between young and elderly males and elimination half-life was unchanged. No dosage adjustment is necessary based on age. In large phase III studies, the concentrations around the time of the end of the infusion in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients.

Pediatric
The pharmacokinetics of moxifloxacin in pediatric subjects have not been studied.

Gender
Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. There are no significant differences in moxifloxacin pharmacokinetics between male and female subjects when differences in body weight are taken into consideration.
A 400 mg single dose study was conducted in 18 young males and females. The comparison of moxifloxacin pharmacokinetics in this study (9 young females and 9 young males) showed no differences in AUC or C_{max} due to gender. Dosage adjustments based on gender are not necessary.

Race
Steady-state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those determined in Caucasians, with a mean C_{max} of 4.1 mg/mL, an AUC_{24} of 47 mg·h/mL, and an elimination half-life of 14 hours, following 400 mg p.o. daily.

Renal Insufficiency
The pharmacokinetic parameters of moxifloxacin are not significantly altered in mild, moderate, severe, or end-stage renal disease. No dosage adjustment is necessary in patients with renal impairment, including those patients requiring hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD).
In a single oral dose study of 24 patients with varying degrees of renal function from normal to severely impaired, the mean peak concentrations (C_{max}) of moxifloxacin were reduced by 21% and 28% in the patients with moderate (CL_{CR} ³ 30 and £ 60 mL/min) and severe (CL_{CR} < 30 mL/min) renal impairment, respectively. The mean systemic exposure (AUC) in these patients was increased by 13%. In the moderate and severe renally impaired patients, the mean AUC for the sulfate conjugate (M1) increased by 1.7-fold (ranging up to 2.8-fold) and mean AUC and C_{max} for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8-fold) and 1.4-fold (ranging up to 2.5-fold), respectively.
The pharmacokinetics of single dose and multiple dose moxifloxacin were studied in patients with CL_{CR} < 20 mL/min on either hemodialysis or continuous ambulatory peritoneal dialysis (8 HD, 8 CAPD). Following a single 400 mg oral dose, the AUC of moxifloxacin in these HD and CAPD patients did not vary significantly from the AUC generally found in healthy volunteers. C_{max} values of moxifloxacin were reduced by about 45% and 33% in HD and CAPD patients, respectively, compared to healthy, historical controls. The exposure (AUC) to the sulfate conjugate (M1) increased by 1.4- to 1.5-fold in these patients. The mean AUC of the glucuronide conjugate (M2) increased by a factor of 7.5, whereas the mean C_{max} values of the glucuronide conjugate (M2) increased by a factor of 2.5 to 3, compared to healthy subjects. The sulfate and the glucuronide conjugates of moxifloxacin are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal disease including those undergoing HD and CAPD has not been studied.
Oral administration of 400 mg QD moxifloxacin for 7 days to patients on HD or CAPD produced mean systemic exposure (AUC_{ss}) to moxifloxacin similar to that generally seen in healthy volunteers. Steady-state C_{max} values were about 22% lower in HD patients but were comparable between CAPD patients and healthy volunteers. Both HD and CAPD removed only small amounts of moxifloxacin from the body (approximately 9% by HD, and 3% by CAPD). HD and CAPD also removed about 4% and 2% of the glucuronide metabolite (M2), respectively.

Hepatic Insufficiency
In 400 mg single oral dose studies in 6 patients with mild (Child Pugh Class A), and 10 patients with moderate (Child Pugh Class B), hepatic insufficiency, moxifloxacin mean systemic exposure (AUC) was 78% and 102%, respectively, of 18 healthy controls and mean peak concentration (C_{max}) was 79% and 84% of controls.
The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging up to 5.9-fold) and 5.7-fold (ranging up to 8.0-fold) in the mild and moderate groups, respectively. The mean C_{max} of M1 increased by approximately 3-fold in both groups (ranging up to 4.7- and 3.9-fold). The mean AUC of the glucuronide conjugate of moxifloxacin (M2) increased by 1.5-fold (ranging up to 2.5-fold) in both groups. The mean C_{max} of M2 increased by 1.6- and 1.3-fold (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. No dosage adjustment is recommended for mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See **POSOLOGY AND METHOD OF ADMINISTRATION**.)

Photosensitivity Potential
A study of the skin response to ultraviolet (UVA and UVB) and visible radiation conducted in 32 healthy volunteers (8 per group) demonstrated that moxifloxacin does not show phototoxicity in comparison to placebo. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo. In this study, the MED measured for both doses of moxifloxacin were not significantly different from placebo, while lomefloxacin significantly lowered the MED. (See **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**.)

Drug-drug Interactions
The potential for pharmacokinetic drug interactions between moxifloxacin and itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, oral contraceptives, ranitidine, glyburide, and calcium has been evaluated. There was no clinically significant effect of moxifloxacin on itraconazole, theophylline, warfarin, digoxin, oral contraceptives, or glyburide kinetics. Itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, ranitidine, and calcium did not significantly affect the pharmacokinetics of moxifloxacin. These results and the data from *in vitro* studies suggest that moxifloxacin is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 enzymes.

cholestatic)
Musculo-skeletal system: Tendon rupture
Skin and appendages: Stevens-Johnson Syndrome
Nervous system: Psychotic reactions
Cardiovascular: Ventricular tachyarrhythmias including torsade de pointes and cardiac arrest have been reported in very rare cases especially in patients with severe underlying proarrhythmic conditions (see also special warnings and precautions for use).

The most common changes in laboratory parameters without regard to drug relationship and which are not listed above as ADRs were:

increased and decreased haematocrit, increased WBC, increased and decreased RBC, decreased blood glucose, decreased haemoglobin, increased alkaline phosphatase, increased SGOT/AST, increased SGPT/ALT, increased bilirubin, increased urea, increased creatinine, increased BUN.

It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

OVERDOSE
Only limited data on overdose are available. Single doses of up to 1200 mg and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status.

The use of charcoal early during absorption after oral administration may be useful to prevent excessive increase of systemic exposure to moxifloxacin. After intravenous drug administration charcoal only slightly reduces systemic exposure (approx. 20%) and is of limited use in case of intravenous overdosing.

POSOLOGY AND METHOD OF ADMINISTRATION

Range of dose (adults)
The recommended dose for moxifloxacin is 400 mg once-daily.

Duration of treatment
The duration of treatment should be determined by the severity of the indication or clinical response. The following general recommendations for the treatment of upper and lower respiratory tract infections are made:
Acute exacerbation of chronic bronchitis: 5 days
Community acquired pneumonia: The recommended total treatment duration for sequential administration (intravenous followed by oral) is 7 - 14 days
Acute sinusitis: 7 days
The recommended duration of treatment in skin and soft tissue infections is 7 days.
Therapy may be initial intravenous administration, followed by oral tablet administration when clinically indicated.
Avelox infusion solution has been studied in clinical trials for up to 14 days treatment.

Method of administration
The infusion solution should be infused intravenously over 60 minutes.
It can be administered directly or together with compatible infusion solutions.
The following coinfusions were found to form stable mixtures over a period of 24 hours at room temperature with moxifloxacin infusion solution, and can therefore be considered as compatible:

- Water for Injections
- Sodium Chloride 0.9%
- Sodium Chloride 1 molar
- Glucose 5%
- Glucose 10%
- Glucose 40%
- Xylit 20%
- Ringer Solution
- Lactated Ringer Solution
- Aminofusin 10% (manufacturer: Pharmacia & Upjohn)
- Jonosteril D5 (manufacturer: Fresenius Kabi)

If moxifloxacin infusion solution is to be given with another drug, each drug should be given separately (see also Incompatibilities).
Only clear solutions are to be used.

Elderly
No adjustment of dosage is required in the elderly.

Children
The use of moxifloxacin in children and adolescents in the growth phase is contraindicated.

Hepatic impairment
No dosage adjustment is required in patients with impaired liver function (see also special warnings and special precautions for use in Child Pugh C patients).

Renal impairment
No dose adjustment is required in patients with any degree of renal impairment (including creatinine clearance ≤ 30 ml/min/1.73m²) and in patients on chronic dialysis i. e. hemodialysis and continuous ambulatory peritoneal dialysis.

Interethnic differences
Possible interethnic differences were examined in Caucasians, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected. Therefore, no adjustment of dosage is required in ethnic groups.

NOTES

Incompatibilities
The following coinfusions were found to be incompatible with moxifloxacin infusion solution:

- Sodium Chloride 10%
- Sodium Chloride 20%
- Sodium Hydrogen Carbonate 4.2%
- Sodium Hydrogen Carbonate 8.4%

INSTRUCTIONS FOR USE/HANDLING
Do not refrigerate or freeze. Store in the original container.
At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution in a refrigerator.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

PRESENTATION
250 ml per flexibag/vial

Bayer HealthCare AG, D-51368 Leverkusen, Germany
AVELOX Infusion Solution 400mg/250ml / OE05_US0604 / TW03 / 092004