速博新® 靜脈輸液 0.1、0.2、0.4 公克
Ciproxin® Inf. Sol. 50ml/100mg、100ml/200mg、200ml/400mg

主成分：ciprofloxacin　　廣效性抗生素　　輸注液　　衛署藥輸字第 018095 號

1. 品名
速博新靜脈輸液50ml/100mg (0.9% NaCl)
速博新靜脈輸液100ml/200mg (0.9% NaCl)
速博新靜脈輸液200ml/400mg (0.9% NaCl)

2. 成份含量
每瓶50毫升的輸注溶液含127.2毫克的ciprofloxacin lactate，相當於100毫克的ciprofloxacin。鈉含量為177毫克(7.7毫莫耳)。
每瓶100毫升的輸注溶液含254.4毫克的ciprofloxacin lactate，相當於200毫克的ciprofloxacin。鈉含量為354毫克(15.4毫莫耳)。
每瓶200毫升的輸注溶液含508.8毫克的ciprofloxacin lactate，相當於400毫克的ciprofloxacin。鈉含量為708毫克(30.8毫莫耳)。

3. 劑型
速博新靜脈輸液50ml/100mg (含0.9% NaCl)：清澈，幾乎無色至淡黃色溶液，pH值3.9-4.5。
速博新靜脈輸液100ml/200mg (含0.9% NaCl)：清澈，幾乎無色至淡黃色溶液，pH值3.9-4.5。
速博新靜脈輸液200ml/400mg (含0.9% NaCl)：清澈，幾乎無色至淡黃色溶液，pH值3.9-4.5。

4. 臨床特性
4.1 適應症
成人
對ciprofloxacin有感受性細菌所引起之呼吸道感染、中耳炎、竇炎、眼感染、腎臟及泌尿道感染(包括淋病)、腹部感染(包括腸炎、膽囊炎、腹膜炎)、皮膚及軟組織感染、骨髓炎、關節感染、菌血症。
[說明]
- 呼吸道的感染
  因肺炎雙球菌(Pneumococcus)引起肺炎之門診病人，ciprofloxacin不應用為第一線治療用藥。而對於治療由克雷白桿菌屬(*Klebsiella* spp.)、大腸桿菌屬(*Enterobacter* spp.)、變形桿菌屬(*Proteus* spp.)、大腸桿菌(*Escherichia coli*)、綠膿桿菌(*Pseudomonas aeruginosa*)、嗜血桿菌屬(*Haemophilus* spp.)、Moraxella catarrhalis、Legionella、及葡萄球菌(Staphylococci)所引起的肺炎，ciprofloxacin則作為合適的治療用藥。
- 中耳(中耳炎)、副鼻竇(鼻竇炎)的感染，尤其是由包括綠膿桿菌(*Pseudomonas aeruginosa*)在內的革蘭氏陰性菌，或葡萄球菌(Staphylococci)所引起。
- 眼部的感染
- 腎和/或泌尿道的感染
- 生殖器官的感染，包括子宮附屬器炎、淋病、前列腺炎
- 腹腔的感染(例如腸胃道、膽管的感染、腹膜炎)
- 皮膚及軟組織的感染
- 骨頭及關節的感染
- 敗血症
- 免疫系統衰弱的病人(如接受免疫抑制治療或處於嗜中性白血球減少狀態的病人)已受感染或具高度被感染危險時的預防
- 對於免疫抑制的病人的選擇性腸內淨化

小孩
- 大腸桿菌(*Escherichia coli*)引起之複雜性泌尿道感染和腎盂腎炎(1-17歲)
- 綠膿桿菌(*P. aeruginosa*)有關之囊腫性纖維化產生急性肺部惡化的現象(5-17歲)
[說明]
因關節及結締組織之併發症發生率較高，本藥非小孩複雜性泌尿道感染之首選藥物。
在小孩的臨床試驗僅針對於上述的適應症，關於其他適應症的臨床使用經驗有限。
由於可能會導致與關節和/或週邊組織有關的不良反應，必須經過審慎的效益/風險評估後才可以使用本品治療。

成人和小孩
- 吸入性炭疽病(接觸後)
[說明]
降低接觸氣霧化的炭疽桿菌後疾病的發生或惡化。
Ciprofloxacin在人體中所到達的血中濃度可以當作一種替代指標，合理地用於預測臨床效益和提供疾病治療的基準。

4.2 劑量與用法《本藥限由醫師使用》
成人
除非有其他處方，建議劑量如下：

	靜脈輸注
呼吸道感染(根據嚴重度及感染病菌)	2 × 200 – 400 mg
泌尿道感染： - 急性、非併發型 - 女性膀胱炎(停經前) - 併發型	 2 × 100 mg 單一劑量100 mg 2 × 200 mg
淋病 - 外生殖器 - 急性、非併發型	 2 × 100 mg 單一劑量100 mg
腹瀉	2 × 200 mg
其他感染(見適應症)	2 × 200 – 400 mg
特別嚴重、會威脅生命的感染。例如 - 鏈球菌感染引起的肺炎 - 囊腫性纖維化的復發感染 - 骨頭及關節的感染 - 敗血症 - 腹膜炎 特別是有假單胞菌屬(Pseudomonas)、葡萄球菌屬(Staphylococcus)和鏈球菌(Streptococcus)存在時。	3 × 400 mg
吸入性炭疽病(接觸後)	2 × 400 mg 當懷疑或確定接觸後，應儘早使用本品治療。

特殊族群：
小孩 (1-17歲)
- 複雜性泌尿道感染和腎盂腎炎
治療複雜性泌尿道感染和腎炎時，每8小時靜脈輸注一次，每次6-10 mg/kg，每次靜脈輸注最大劑量是400毫克。
- 囊腫性纖維化
臨床和藥物動力學資料證明ciprofloxacin在綠膿桿菌有關之急性肺部惡化的小兒囊腫性纖維化(年齡5-17歲)的靜脈輸注劑量是每天三次，每次10 mg/kg (每天最大劑量1200毫克)。
- 吸入性炭疽病(接觸後)
每天兩次每次靜脈輸注10 mg/kg，每次靜脈輸注最大劑量不得超過400 mg (每天最大劑量是800 mg)。
當懷疑或確定接觸後，應儘早使用本品治療。

老年人(> 65歲)
老年人必須依據其病情嚴重性和肌氨酸酐清除率(creatinine)給予最低的藥量。

腎及肝功能受損的病患
成人：
◆腎功能受損
- 當creatinine清除率在31到60 ml/min/1.73m^{2}或血漿中creatinine的濃度在1.4到1.9 mg/100 ml時，靜脈注射每日最大劑量為一天800毫克。
- 當creatinine清除率少於30 ml/min/1.73m^{2}或血漿中creatinine的濃度等於或高於2.0 mg/100 ml時，靜脈注射每日最大劑量為一天400毫克。
◆腎功能受損且須血液透析
- 當creatinine清除率在31到60 ml/min/1.73m^{2}或血漿中creatinine的濃度在1.4到1.9 mg/100 ml時，靜脈注射每日最大劑量為一天800毫克 。
- 當creatinine清除率少於30 ml/min/1.73m^{2}或血漿中creatinine的濃度等於或高於2.0 mg/100 ml時，靜脈注射每日最大劑量為一天400毫克，於透析完再給藥。
◆腎功能受損且進行連續性腹膜透析之門診病人(CAPD)
將Ciprofloxacin輸注液加入透析液內(腹膜內)：每升透析液加入50毫克的ciprofloxacin，每6小時一次，一天4次。
◆肝功能受損
不須調整劑量。
◆腎及肝功能受損
- 當creatinine清除率在31到60 ml/min/1.73m^{2}或血漿中creatinine的濃度在1.4到1.9 mg/100 ml時，靜脈注射每日最大劑量為一天800毫克 。
- 當creatinine清除率少於30 ml/min/1.73m^{2}或血漿中creatinine的濃度等於或高於2.0 mg/100 ml時，靜脈注射每日最大劑量為一天400毫克。

小孩：
腎功能受損或肝功能受損小孩的使用劑量尚未被研究。

給藥方法
速博新靜脈輸液必須經由靜脈輸注，並且輸注時間要超過60分鐘。緩慢的將藥打入大的靜脈，可以減少病人的不適及降低靜脈刺激的危險性。可以直接給藥或與其它相容的輸注溶液混合後給藥。
Ciprofloxacin輸注液與生理食鹽水、林格氏液、乳酸林格氏液、5%或10%葡萄糖溶液、10%果糖溶液和含0.225%或0.45%氯化鈉的5%葡萄糖溶液相容。由於微生物學及光敏感度的考量，當ciprofloxacin輸注液與相容的輸注液混合後，必須在最短的時間內使用。
除非ciprofloxacin與其他輸注液或藥品的相容性得到證實，否則ciprofloxacin應與這些溶液分開給予。可目視辨別的不相容的徵狀包括：沉澱、雲狀物及變色。所有輸注液或藥品其物理或化學性質在溶液(如penicillin、heparin溶液)的pH下為不安定時，不相容性就會產生。特別是要混合的輸注液其pH值是鹼性時(Ciprofloxacin輸注液的pH值為3.9–4.5之間)。

治療期
治療期間的長短由疾病的嚴重程度及臨床和細菌生長的週期決定。在發燒或臨床症狀消失後須持續給藥至少三天。平均治療期為：

成人
- 急性、非併發型淋病及膀胱炎為1天
- 腎、泌尿道和腹腔感染可高達7天
- 身體防禦力弱的病人在整個嗜中性白血球減少的期間都要用藥
- 骨髓炎病人最多2個月
- 其它感染為7–14天
在鏈球菌的感染時，因會有續發併發症的危險，所以治療必須持續至少10天。由披衣菌所引起的感染，治療也必須持續至少10天。

小孩 (1-17歲)
- 複雜性泌尿道感染和腎盂腎炎
大腸桿菌(*Escherichia coli*)引起之複雜性泌尿道感染和腎盂腎炎，治療期是10-21天。
- 囊腫性纖維化
綠膿桿菌有關之囊腫性纖維化的急性肺部惡化的病童(年齡5-17歲)，必須持續治療10-14天。

成人和小孩
- 吸入性炭疽病(接觸後)
Ciprofloxacin (靜脈注射或口服)治療炭疽桿菌(接觸後)的總治療期是60天。

4.3 禁忌
Ciprofloxacin不可使用於對ciprofloxacin、其他quinolone類藥物或任何賦形劑會過敏的病人(參見"賦形劑")。
禁止同時使用ciprofloxacin和tizanidine (參見"與其他藥物和其他形式的交互作用")。

4.4 警語及注意事項
嚴重感染和/或格蘭氏陽性或厭氧菌感染
嚴重感染、格蘭氏陽性或厭氧菌感染不適合單獨使用ciprofloxacin治療，治療這些感染時， ciprofloxacin 應併用其他適當的抗細菌製劑。

肺炎鏈球菌感染
Ciprofloxacin不建議用於肺炎鏈球菌的感染，因為對抗肺炎鏈球菌的療效有限。

生殖道感染
生殖道感染可能是由對fluoroquinolone具有抗藥性的淋病雙球菌分離株(Neisseria gonorrhoeae isolates)所導致，當生殖道感染被認為或已知是淋病雙球菌感染時， 特別重要的是須獲取當地對ciprofloxacin抗藥性的流行率資訊和依據實驗室測試結果確認細菌的感受性。

心臟疾病
Ciproxin與QT延長有關(參見"不良反應")。由於女性相較於男性有較長的QTc間隔基準值(Baseline QTc interval)，所以對於會延長QTc間隔的藥品可能會較為敏感。老年病患可能也較容易受到藥品影響QT區間，當Ciproxin併用會導致QT區間延長的藥物(例如：class IA or III的抗心律不整藥物、三環抗憂鬱劑、巨環類抗生素、抗精神病藥物) (參見與其他藥物和其他形式的交互作用)或病患潛在有QT間隔延長或torsade de points危險因子(例如：先天性QT延長症候群、未經控制的電解質失調[例如：低血鉀症或低血鎂症]及心臟疾病[例如心衰竭、心肌梗塞或心搏徐緩)時須謹慎使用。

小孩和青少年 (1-17歲)
依據藥品的等級，ciprofloxacin已被指出會導致發育未完全動物其承受重量的關節產生關節病變，從使用ciprofloxacin的病患(年齡小於18歲; 大多數是囊腫性纖維化病患)其可取得的安全性資料分析，並無任何證據顯示與藥物有關的軟骨或關節傷害產生，目前尚無Ciproxin使用於治療綠膿桿菌引起的囊腫性纖維化產生急性肺部惡化(小孩年齡5-17歲)、大腸桿菌所引起之複雜性泌尿道感染和腎盂腎炎(小孩年齡1-17歲)和吸入性炭疽病(接觸後)之外其他適應症的研究，至於其他疾病，其臨床經驗有限。
針對吸入性炭疽病(接觸後)，風險/效益評估顯示孩童病患使用ciprofloxacin治療是適當的。

過敏反應
在某些例子中，第一次給予ciprofloxacin後會產生過敏反應(參見"不良反應")，須立刻通知醫生。
在極少數的情況下，過敏性及類過敏性反應會變成具生命危險性的休克(參見"不良反應")。在這些情況下，Ciproxin必須停藥，並進行藥物治療(如休克的治療)。

腸胃系統
在治療期或治療後有嚴重且持續性的腹瀉，必須請教醫生，因為在這個症狀背後，可能隱藏著嚴重的抗生素相關腸炎(威脅生命的偽膜性結腸炎，有可能致死)，需立即治療(參見"不良反應")。在這種情況下，必須停用Ciproxin並給予適當的治療(例如：每日口服4 x 250 毫克 的vancomycin)，禁用抑制蠕動的藥物。

肝膽系統
已經有使用Ciproxin發生肝壞死(hepatic necrosis)和肝衰竭而危及生命的案例通報。若產生任何肝臟疾病的徵兆及症狀(例如：食慾不振、黃疸、深色尿液、皮膚騷癢或腹部壓痛感)， 應該要中斷治療(請見"不良反應")。使用Ciproxin治療的患者，其轉氨酶(transaminases)、鹼性磷酸酶(alkaline phosphatase)、或膽汁鬱滯性黃疸(cholestatic jaundice)會暫時升高，特別是之前就有肝受損的病人。

肌肉骨骼系統
***衛生署公告之警語：本藥品具有使重症肌無力惡化之風險，具有重症肌無力患者應避免使用。**
使用Ciproxin的患者，即使是在治療開始的48小時內，可能會發生肌腱炎和肌腱斷裂(主要是跟腱) (有時為雙側性)。肌腱的發炎和斷裂甚至可能會發生在停止Ciproxin治療後的數個月。
老年人或同時併用皮質類固醇治療的患者可能會增加發生肌腱病變(tendinopathy)的風險。
若有任何肌腱炎的跡象(如疼痛性腫脹、發炎)，應通知醫生並且停止使用ciprofloxacin，小心照護保持四肢處於休息狀態，避免不適當的身體運動(否則會增加肌腱斷裂的危險）。
肌腱斷裂(主要是阿基里斯腱)常發生在之前曾使用醣質類固醇全身性治療的老年人。
Ciproxin必須小心的使用在曾經因為服用quinolone治療導致肌腱疾病的病患。

神經系統
Ciproxin和其它的Fluoroquinolones相似，已知會誘發癲癇或降低癲癇閾值。對於癲癇病人及曾患有中樞神經失調的病人(例如痙攣閾值偏低、曾有痙攣的病史、腦部血流減少、腦部結構改變或中風)，Ciproxin應只用在治療效益大於危險性的情況下，因為這些病人面臨著可能發生中樞神經失調的危險。已有癲癇重積狀態(status epilepticus)的通報案例(參見"不良反應")。 如果發生癲癇應該中斷Ciproxin治療。
在某些例子中，第一次給予Fluoroquinolones (包括ciprofloxacin)後甚至可能會發生精神病學反應(Psychiatric reactions)。在少數的情況，抑鬱或精神病反應可能會演變成自殺意念/想法和自我傷害的行為，例如自殺未遂或完全自殺(請見"不良反應")。當患者產生任何這些反應，ciprofloxacin必須停藥，給予適當處置。
當患者服者使用包括Ciproxin的Fluoroquinolones，曾有感覺或感覺運動神經產生多發性神經病變(polyneuropathy)造成感覺異常、感覺遲鈍及感覺減退的案例通報。正在使用Ciproxin治療的患者，如果發生神經病變的症狀(例如：疼痛、燒灼感、刺痛感、麻痺或虛弱感)，在繼續治療前應該先告知醫生。

皮膚與附屬器官
Ciprofloxacin會產生光敏感反應。服用Ciproxin的病患應避免暴露於過量的陽光及紫外線下。若有光過敏作用(如像曬傷般的皮膚反應)產生，須停止給藥(參見"不良反應")。

Cytochrome P450
Ciprofloxacin已知是CYP 450 1A2酵素的中度抑制劑，當與其他經由此酵素代謝途徑的藥物(例如：tizanidine、 theophylline、methylxanthines、caffeine、duloxetine、ropinirole、clozapine、olanzapine)併用時需小心，因為ciprofloxacin會抑制其代謝清除率，導致與血漿濃度增加有關的藥物副作用產生(參見"與其他藥物和其他形式的交互作用")。

注射部位的反應
Ciprofloxacin以靜脈注射的方式給藥，曾被報告過在注射部位會產生局部反應。若輸注時間等於30分鐘或更少，這些反應更容易發生。這些局部的皮膚反應在輸注結束後會很快的緩解。除非反應重覆出現或惡化，否則後續的靜脈給藥並不是禁忌。

檢驗的相互影響
Ciprofloxacin在體外的藥效會藉由抑制結核分歧桿菌(*Mycobacterial tuberculosis*)生長，干擾分枝桿菌屬(*Mycobacterium spp.*)培養的檢測，導致服用ciprofloxacin的病患產生偽陰性反應。

4.5 與其他藥物和其他形式的交互作用
已知會延長QT間隔的藥物
Ciproxin和其它的Fluoroquinolones一樣，對於併用已知會延長QT間隔的藥物(例如：class IA或III抗心律不整藥物(例如：class IA or III的抗心律不整藥物、三環抗憂鬱劑、巨環類抗生素、抗精神病藥物)時，須謹慎使用。(參見 "警語及注意事項")

Probenecid
Probenecid會干擾Ciprofloxacin的腎排除，所以併用Ciproxin和probenecid會增加Ciprofloxacin的血中濃度。

Tizanidine
健康受試者的臨床試驗顯示，當併用ciprofloxacin和tizanidine時，Tizanidine的血漿濃度會上升【C_{max}增加7倍，範圍： 4-21倍；AUC增加10倍，範圍：6-24倍】，導致增強低血壓和鎮靜的作用(參見 "警語及注意事項- Cytochrome P450")，所以含有tizanidine的藥物不可以和Ciproxin同時使用(參見"禁忌")。

Theophylline
Ciprofloxacin和含有theophylline的藥物一起服用會使theophylline的血中濃度增加，導致theophylline引發的副作用；在極少數的情況下，這些副作用會造成生命危險或致命的。如果無法避免併用此兩種藥物，應監測血中theophylline濃度且適當減少theophylline的劑量。(參見 "警語及注意事項- Cytochrome P450")

其他xanthine的衍生物
Ciprofloxacin與含有caffeine或pentoxifylline (oxpentifylline)的藥物併用時，已知會增加xanthine衍生物的血中濃度。

Phenytoin
在同時併用Ciproxin及phenytoin的患者觀察到phenytoin的血漿濃度會改變(降低或增加)。
為了避免因降低phenytoin的血漿濃度而造成對癲癇失去控制，以及預防當原本併用此兩種藥品的患者中斷使用Ciproxin，造成phenytoin過量產生的不良反應，建議併用Ciproxin及phenytoin的期間以及中斷併用之後要監測phenytoin的治療(包括測量phenytoin的血漿濃度)

Methotrexate
Methotrexate在腎小管的輸送可能因併服Ciproxin而受到抑制，導致methotrexate血漿濃度增加，這可能增加methotrexate所引起毒性反應的危險性，因此，使用methotrexate治療的病人，當要併服Ciproxin時，必須小心監測。

NSAID
動物研究顯示非常高劑量的quinolones藥物(gyrase抑制劑)和某些非固醇類抗發炎藥物(acetylsalicylic acid除外)併用會引起痙攣。

Cyclosporin
Ciprofloxacin和含有cyclosporin的藥物併用會造成血中肌氨酸酐濃度的暫時性升高。因此，需時常(一星期二次)控制這類病患血中肌氨酸酐的濃度。

維他命K拮抗劑
同時使用Ciproxin和維他命K拮抗劑時會增加抗凝血的作用，此風險會因為潛在的感染、年齡和病患的狀態而不同，所以ciprofloxacin對於INR (international normalized ratio)增加的影響難以評估，併用ciprofloxacin與維他命K拮抗劑(例如：warfarin、acenocoumarol、phenprocoumon或fluindione)時需頻繁地監測INR。

口服降血糖製劑
曾有併用Ciproxin及口服降血糖製劑(主要為sulfonylureas，例如：glibenclamide, glimepiride)產生低血糖的案例通報。推測可能是由於增強口服降血糖製劑的作用。(參見 "不良反應")

Duloxetine
臨床研究顯示當duloxetine和CYP450 1A2 isozyme的強抑制劑例如：fluvoxamine併用時，會導致duloxetine的AUC和C_{max}增加，雖然沒有臨床資料可以證明fluvoxamine和ciprofloxacin可能的交互作用機轉，相似的結果可被預期在藥物併用時(參見"警語及注意事項- Cytochrome P450")。

Ropinirole
一個臨床研究顯示當ropinirole和ciprofloxacin (CYP450 1A2 isozyme中度抑制劑)併用時，會導致ropinirole的C_{max}和AUC分別增加60%和84%，與Ciproxin併用時需監控ropinirole相關的不良反應，建議適時的調整劑量(參見"警語及注意事項- Cytochrome P450")。

Lidocaine
健康受試者併用含有lidocaine的藥物和ciprofloxacin (CYP450 1A2 isozyme中度抑制劑)時，靜脈注射lidocaine的清除率會減低22%，雖然lidocaine治療的耐受性佳，併用時會有與ciprofloxacin相關的副作用發生。

Clozapine
併用250毫克ciprofloxacin和clozapine7天後，clozapine和N-desmethylclozapine的血中濃度會分別增加29%和31%，與Ciproxin併用後建議需進行臨床監測和適當的調整clozapine的劑量(參見"警語及注意事項- Cytochrome P450")。

Sildenafil
口服併用50毫克的sildenafil和500毫克的ciprofloxacin後，健康受試者的sildenafil C_{max}和AUC會增加約2倍，因此併用Ciproxin和sildenafil時，sildenafil劑量需考慮減半。

4.6 懷孕與授乳
懷孕
Ciprofloxacin在懷孕婦女的安全性尚未建立。動物試驗未顯示有生殖毒性。根據動物試驗的結果，可能無法排除藥物可能會對尚未成熟生物的關節軟骨造成傷害。(參見 "臨床前安全性資料")，因此Ciproxin不建議在懷孕期間使用。動物實驗至今尚未有致畸胎(畸形)的證據(參見 "臨床前安全性資料")。

哺乳
Ciprofloxacin會分泌到乳汁中，由於有關節軟骨傷害的潛在風險，哺乳婦女不建議使用ciprofloxacin (參見"臨床前安全性資料")。

4.7 駕駛及操作機械的能力
Fluoroquinolones (包含ciprofloxacin)會影響中樞神經的反應導致病患駕駛或操作機械的能力會有損害(參見"不良反應")，尤其與酒精併用時更易發生。

4.8 不良反應
- 安全資訊摘要
藥物不良反應(ADR)根據ciprofloxacin (口服、注射)的所有臨床研究，以CIOMS III發生率分類(n=51621位病人)。
- 不良反應列表
已報導與Ciproxin有關的不良藥物反應摘要在下表中，在每一個發生頻率分類中，不良反應的表示依據嚴重程度的順序刊載：

發生頻率定義：
非常常見 (≥1/10）
常見 (≥1/100 至 <1/10)
不常見 (≥1/1,000 至 <1/100)
少見 (≥1/10,000 至 <1/1,000)
罕見 (≤1/10,000)
不良藥物反應發生在藥品上市後且發生頻率無法預期時，將列在 "未知"。

	常見	不常見	少見	罕見	未知
感染		念珠菌感染	抗生素相關性結腸炎（致死性極低）		
血液及淋巴系統		嗜伊紅血球增多	白血球減少、貧血、嗜中性白血球低下、白血球增多、血小板減少、血小板過多	溶血性貧血、顆粒性血球減少、全血球減少（有生命危險的）、骨髓抑制（有生命危險的）	
免疫系統			過敏反應、過敏性水腫/血管性水腫	過敏性反應、過敏性休克（有生命危險的）、類血漿疾病反應（serum sickness – like reaction）	
代謝及營養失調		降低食慾和食物攝取	血糖過高 血糖過低		
精神疾病		精神運動性過度活躍/易激動	精神混亂及方向迷失、焦慮、不正常的作夢（惡夢）、抑鬱（潛在性累積自殘行為，例如：自殺意念/想法，企圖自殺或完全自殺）、幻覺	精神上的反應（潛在性累積自殘行為，例如：自殺意念/想法，企圖自殺或完全自殺）	
神經系統疾病		頭痛、暈眩、失眠、味覺喪失	感覺異常/遲鈍、感覺減退、震顫、癲癇發作（包括癲癇重積狀態）、眩暈	偏頭痛、運動失調、嗅覺喪失、感覺過敏、顱內壓增高（大腦假性腫瘤）	週邊神經病變和多發性神經病變
眼部疾病			視力障礙	辨色扭曲	
耳部疾病			耳鳴、聽力減弱	聽力喪失	
心臟疾病			心跳加快		QT延長、心室心律不整、torsades de points*
血管疾病			血管擴張、低血壓、暈厥	血管炎	
呼吸道、胸部及縱膈腔			呼吸困難（包含類似氣喘的症狀）		
胃腸道疾病	噁心、腹瀉	嘔吐、胃腸道及腹部疼痛、消化不良、胃腸脹氣		胰臟炎	
肝膽疾病		轉胺酶增加、膽紅素增加	肝功能損害、黃膽、肝炎（非傳染性）	肝壞死（只有很少的機會會轉變成有生命危險的肝衰竭）	
皮膚及皮下組織		紅疹、搔癢、蕁麻疹	光敏感反應、水泡	瘀點、多型性紅斑、結節性紅斑、Stevens-Johnson症狀（有生命危險的）、毒性表皮壞死溶解症（有生命危險的）	急性廣泛性發疹性膿疱症(AGEP)
肌肉骨骼和結締組織		關節痛	肌肉酸痛、關節炎、肌肉張力增加及痙攣	肌肉無力、肌腱炎、肌腱斷裂（主要是Achilles肌腱）、重症肌無力的惡化	
腎臟及泌尿系統		腎功能異常	腎衰竭、血尿、結晶尿、腎小管間質腎炎		
一般症狀		非特定區域疼痛、感覺不舒服、發熱	水腫、出汗（多汗症）	步履不穩	
Investigations		血液中鹼性磷酸酶增加	凝血原值不正常、澱粉水解酵素升高		INR(International normalized ratio)值增加（使用維生素K拮抗劑治療的患者）

* 事件發生在藥品上市後而且顯著的發生在有QT 延長風險的病患（參見"警語及注意事項"）。

下列不良反應在接受靜脈輸注或靜脈輸注後轉口服治療的病患，有較高的發生頻率：

常見	嘔吐、短暫性轉胺酶上升、紅疹
不常見	血小板減少症、血小板過多、精神混亂及方向迷失、幻覺、感覺異常/遲鈍、癲癇發作、眩暈、視力障礙、聽力喪失、心跳加快、血管擴張、低血壓、短暫肝功能損害、黃疸、腎衰竭、水腫
少見	全血球減少症、骨髓抑制、過敏性休克、精神上的反應、偏頭痛、嗅覺喪失、聽力受損、血管炎、胰臟炎、肝壞死、瘀點、肌腱斷裂

MedDRA preferred term是用來描述某些反應和其相同含義及相關狀況的詞彙。ADR term則表示依據MedDRA version 14.0 (除了黴菌重覆感染和不特定疼痛)的詞彙

特殊族群的額外資訊
小孩病患
有一項針對1至17歲兒童的研究評估肌肉骨骼的不良作用，包括關節痛、異常步態、關節檢查異常等，在開始治療6週時，這些不良作用的發生率在ciprofloxacin組高於對照藥物。(參見"警語及注意事項")。
之前提及關節病的發生機率是從成人的試驗所收集到的資料來計算。在小孩的族群，關節病的發生機率為常見(參見"警語及注意事項")

過量
除了一般急救措施外，還建議監測腎功能，包括尿液pH值。可以使尿液酸化，以預防結晶尿。患者應該維持在足夠的水份補充狀態。在過量時，含鈣或鎂的制酸劑可能可以減少ciprofloxacin的吸收。
只有少量的Ciprofloxacin (＜10%)會在血液透析或腹膜透析排除。

5. 藥理學特性
5.1 藥效學特性
Ciprofloxacin是一合成的廣效性抗生素。

作用機轉：
在體外實驗中ciprofloxacin可以有效對抗所有的革蘭氏陰性病原菌，ciprofloxacin的殺菌作用是因為抑制細菌DNA複製、轉錄、修補和重組時的type II topoisomerase (DNA gyrase和topoisomerase IV)。

抗藥機轉：
Ciprofloxacin的體外抗藥性通常是由於細菌topoisomerases IV和DNA gyrase透過多重步驟突變在作用點突變，單點突變可能會導致感受性減低而非臨床抗藥性，但是多重突變通常會導致臨床上對ciprofloxacin抗藥性及quinolone類的交互抗藥性。
抗藥性機轉使得其他抗生素失去活性，例如：細菌的滲透性屏障(通常是綠膿桿菌)和或輸出幫浦的表現可能會影響對ciprofloxacin的感受性，gnr基因所產生基因質體媒介的抗藥性已被報導，對於penicillins、cephalosporins、aminoglycosides、marolides和tetracyclines的抗藥性機制不會影響ciprofloxacin的抗菌活性，而且尚未ciprofloxacin和其他抗菌藥品的交互抗藥，對上述藥品具有抗藥性的細菌可能會對ciprofloxacin具有感受性。
最小殺菌濃度(MBC)通常不會超過2個係數的最小抑菌濃度(MIC)。
對ciprofloxacin的體外感受性：
抗藥性的流行率會因地理環境的不同和所選擇菌種的時間而不同，當地抗藥性的資料是需要的，特別是治療嚴重感染時，必要時或對某些感染不確定時，需請教專家的意見，了解本土抗藥性流行率作為用藥參考。
以下所列的微生物菌屬或菌種在體外對ciprofloxacin具有感受性：

革蘭氏陽性嗜氧菌
Bacillus anthracis
Staphylococcus aureus (methicillin感受性菌株)
Staphylococcus saprophyticus
Streptococcus pyogenes

革蘭氏陰性嗜氧菌

Aeromonas spp.	*Moraxella catarrhalis*
Brucella spp.	*Neisseria meningitidis*
Citrobacter koseri	*Pasteurella spp.*
Francisella tularensis	*Salmonella spp.**
Haemophilus ducreyi	*Shigella spp.*
Haemophilius influenzae	*Vibrio spp.*
Legionella spp.	*Yersinia pestis*

厭氧菌
Mobiluncus

其他病原菌
Chlamydia trachomatis
Chlamydia pneumoniae
Mycoplasma hominis
Mycoplasma pneumoniae

以下這些菌種對Ciprofloxacin呈現不同程度的敏感度：*Acinetobacter baumannii, Burkholderia cepacia, Campylobacter spp., Citrobacter freudii, Enterococcus faecalis, Enterobacter aerogenes, Enterobacter clocae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Providencia spp., Pseudomonas aeruginosa, Pseudomonas fluorescens, Serratia marcescens, Peptostreptococcus spp., Propionibacterium acnes.*

以下這些菌種被認為本身對Ciprofloxacin具有抗藥性：*Staphylococcus aureus* (methicillin-resistant) and *Stenotrophomonas maltophilia, Actinomyces, Enteroccus faecium, Listeria monocytogenes, Mycoplasma genitalium , Ureaplasma urealitycum,* Anaerobic microorganisms (Excepted *Mobiluncus, Peptostreptococus, Propionibacterium acnes*)

5.2 藥動學特性
吸收
靜脈輸注ciprofloxacin後，其平均血中最大濃度在輸注結束時達到，在靜脈輸注400毫克的劑量範圍內，ciprofloxacin的藥物動力學是呈線性的。

分佈
Ciprofloxacin與蛋白質結合率很低(20-30%)，而且在血漿中大部分以非離子狀態存在，ciprofloxacin可以自由地擴散至血管外，最大穩定狀態分佈體積是2-3 L/kg，顯示ciprofloxacin擴散至組織所產生的濃度明顯的超過血漿中的濃度。

代謝
已知會有少量的4種代謝物存在，如下：
Desethyleneciprofloxacin (M1)、sulphociprofloxacin (M2)、oxociprofloxacin (M3)和formylciprofloxacin (M4)，M1到M3代謝物顯示有相當或稍差於nalidixic的體外抗菌活性，M4 (存在量最低的代謝物)主要與norfloxacin具有相等的體外抗菌活性。

排除
Ciprofloxacin主要以非代謝的型態經由腎臟排除，少量經由非腎臟排除。

小孩
在一項小孩的試驗顯示C_{max}和AUC與年齡無關，多次給藥(10 mg/kg/TID)時並未觀察到C_{max}和AUC明顯的增加，10位患有嚴重敗血症的小孩，以10 mg/kg靜脈輸注1小時後，年齡小於1歲者其C_{max}是6.1 mg/L (範圍4.6-8.3 mg/L)；年齡1-5歲者其C_{max}是7.2 mg/L (範圍4.7-11.8 mg/L)，兩組年齡層的AUC值分別是17.4 mg*h/L (範圍11.8-32.0 mg*h/L)和16.5 mg*h/L (範圍11.0-23.8 mg*h/L)，這些數值介於成人治療劑量的範圍內，針對各種感染的小孩病患其族群藥動學分析，小孩的平均半衰期預估值大約是4-5小時，口服懸浮液的生體可用率大約是60%。

5.3 臨床前安全性資料
急性毒性
口服ciprofloxacin的急性毒性可視為非常低。依人種不同，靜脈輸注ciprofloxacin的半數致死劑量為 125 – 290 mg/kg。

慢性毒性
六個月以上的慢性耐受研究
劑量分別增加到500 mg/kg (大鼠)及30 mg/kg (猴子)仍可以耐受且無傷害。猴子最高劑量組(90 mg/kg)觀察到腎小管末稍有變化。

致癌性
小鼠試驗(21個月大，劑量最高到約1000 mg/kg bw/day)及大鼠試驗(24個月大，劑量125 mg/kg bw/day，22星期後調高到250 mg/kg bw/day)皆未顯示任何致癌性的可能。

生殖毒性
大鼠繁殖力試驗
成鼠的繁殖力、子宮及產後的發展及其第一代後代的繁殖力皆未受到ciprofloxacin影響。

胚胎毒性
未有任何證據顯示ciprofloxacin有胚胎毒性或致畸胎毒性作用。

大鼠出生前後及產後的發展
未發現動物出生前後或產後的發展有受到影響。撫養期結束時的組織學研究並未發現有成鼠關節傷害的跡象。

致突變性
有八個ciprofloxacin的體外致突變性實驗已完成。
雖然其中兩個體外實驗(the Mouse Lymphona Cell Forward Mutation Assay及Rat Hepatocyte Primary Culture DNA Repair Assay (UDS))顯示是有致突變性的，但所有的體內試驗包括所有相關指標皆顯示沒有致突變性。

關節耐受性研究
如同其他已知的gyrase抑制劑，ciprofloxacin對未發育完成的動物較大且負重的關節產生傷害。
依年齡、種族及劑量不同對軟骨造成傷害程度也不同，對關節的負重減輕可以減少傷害。發育成熟的動物(大鼠、狗)研究並未有證據顯示軟骨損害。小獵犬的研究顯示給予高劑量(治療劑量的1.3到3.5倍)的ciprofloxacin兩個星期後並觀察5個月，發現有關節損害。但在治療劑量並沒有此現象。

6. 藥劑特性
賦形劑
Lactic acid,
Sodium chloride,
Hydrochloric acid concentrated,
Water for injections

調配禁忌
Ciproxin輸注液與生理食鹽水、林格氏液、乳酸林格氏液、5%或10%葡萄糖溶液、10%果糖溶液和含0.225%或0.45%氯化鈉的5%葡萄糖溶液相容。由於微生物學及光敏感度的考量，當Ciproxin輸注液與相容的輸注液混合後，必須在最短的時間內使用。
除非ciprofloxacin與其他輸注液或藥品的相容性得到證實，否則ciprofloxacin應與這些溶液分開給予。可目視辨別的不相容的徵狀包括：沉澱、雲狀物及變色。所有輸注液或藥品其物理或化學性質在溶液(如penicillin、heparin溶液)的pH下為不安定時，不相容性就會產生。特別是要混合的輸注液其pH值是鹼性時(Ciproxin輸注液的pH值為3.9–4.5之間)。

注意事項
須避光，不可冷藏或冷凍。
因為本藥的輸注液具光敏感度，所以藥瓶須在使用前再從盒子拿出來。在白晝光線下，完整的效力只能保證維持3天。
為了使用上的安全，必須穿刺輸注瓶塞的中央圓圈中，穿刺在圓圈外可能會導致瓶塞受損。

操作說明
低溫儲存環境可能會產生沉澱，但在室溫下(15-25℃)會再度溶解。所以不須將此輸注液置於冰箱儲存。
藥物應置於小孩拿不到的地方。
過期後不可繼續使用。

包裝
50 ml (100 mg), 100 ml (200 mg), 200 ml (400 mg)小瓶裝(vial)

製造廠：Bayer Pharma AG
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

Ciproxin inf. sol. 50ml/100mg, 100ml/200mg, 200ml/400mg / CCDS16 / TW07 / 122012

Ciproxin® Inf. Sol.

50ml/100mg, 100ml/200mg, 200ml/400 mg

Active ingredient: ciprofloxacin | Broad-spectrum antibiotic | Infusion solution

1. NAME OF THE MEDICINAL PRODUCT
Ciproxin 100 mg solution for infusion (0.9% NaCl)
Ciproxin 200 mg solution for infusion (0.9% NaCl)
Ciproxin 400 mg solution for infusion (0.9% NaCl)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Ciproxin inf. sol. 50ml/100mg:
Each glass bottle with 50 ml infusion solution contains 127.2 mg ciprofloxacin lactate, corresponding to 100 mg ciprofloxacin. The sodium content is 177 mg (7.7 mmol).
Ciproxin inf. sol. 100ml/200mg:
Each glass bottle with 100 ml infusion solution contains 254.4 mg ciprofloxacin lactate, corresponding to 200 mg ciprofloxacin. The sodium content is 354 mg (15.4 mmol).
Ciproxin inf. sol. 200ml/400mg:
Each glass bottle with 200 ml infusion solution contains 508.8 mg ciprofloxacin lactate, corresponding to 400 mg ciprofloxacin. The sodium content is 708 mg (30.8 mmol).

3. PHARMACEUTICAL FORM
Ciproxin inf. sol. 50ml/100mg (with 0.9% NaCl):
Clear, nearly colourless to slightly yellowish solution.
The pH-value of the solution for infusion ranges from 3.9 to 4.5.
Ciproxin inf. sol. 100ml/200mg (with 0.9% NaCl):
Clear, nearly colourless to slightly yellowish solution.
The pH-value of the solution for infusion ranges from 3.9 to 4.5.
Ciproxin inf. sol. 200ml/400mg (with 0.9% NaCl):
Clear, nearly colourless to slightly yellowish solution.
The pH-value of the solution for infusion ranges from 3.9 to 4.5.

4. CLINICAL PARTICULARS
4.1 INDICATION(S)
Adults
UNCOMPLICATED AND COMPLICATED INFECTIONS CAUSED BY CIPROFLOXACIN SUSCEPTIBLE PATHOGENS.
- Infections of the respiratory tract
  In the treatment of outpatients with pneumonia due to Pneumococcus, ciprofloxacin should not be used as a first choice of drug.
  Ciprofloxacin can be regarded as an advisable treatment for pneumonias caused by *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Escherichia coli*, *Pseudomonas aeruginosa*, *Haemophilus* spp., *Moraxella catarrhalis*, *Legionella*, and Staphylococci.
- Infections of the middle ear (otitis media), of the paranasal sinuses (sinusitis), especially if these are caused by Gram-negative organisms including *Pseudomonas aeruginosa* or by Staphylococci.
- Infections of the eyes
- Infections of the kidneys and/or the efferent urinary tract
- Infections of the genital organs, including adnexitis, gonorrhoea, prostatitis
- Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis)
- Infections of the skin and soft tissue
- Infections of the bones and joints
- Sepsis
- Infections or imminent risk of infection (prophylaxis) in patients whose immune system has been weakened (e.g. patients on immunosuppressants or have neutropenia)
- Selective intestinal decontamination in immunosuppressed patients

Children
- Treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli* (age range applied in clinical studies: 1-17 years)
- Acute pulmonary exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa* (aged range applied in clinical studies: 5-17)

Ciprofloxacin is not the first choice for the treatment of complicated urinary tract infections in children, because high incident rate of complication on the joints and connective tissue.
The clinical trials in children were performed in the indications listed above. For other indications clinical experience is limited.
Treatment should only be initiated after careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissues.

Inhalational Anthrax (Post-exposure) in Adults and in Children
To reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis.
Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

4.2 DOSAGE AND METHOD OF ADMINISTRATION
Dosage regimen
Adults
Unless otherwise prescribed, the following daily doses are recommended for:

	Intravenous
Respiratory tract infection (according to severity and organism)	2 x 200-400 mg
Urinary tract infections: - acute, uncomplicated - cystitis in women (before menopause) - complicated	 2 x 100 mg single dose 100 mg 2 x 200 mg
Gonorrhea - extragenital - acute, uncomplicated	 2 x 100 mg single dose 100 mg
Diarrhea	2 x 200 mg
Other infections (see Indications)	2 x 200-400 mg
Particularly severe, life threatening infections, i.e. - Streptococcal pneumonia - Recurrent infections in cystic fibrosis - Bone and joint infections - Septicemia - Peritonitis In particular when *Pseudomonas, Staphylococcus* or Streptococcus is present	3 x 400 mg
Inhalational anthrax (post-exposure)	2 x 400 mg Drug administration should begin as soon as possible after suspected or confirmed exposure.

Additional information on special population
Children (1-17 ages)
- Complicated urinary tract infections and pyelonephritis
  For complicated urinary tract infections or pyelonephritis the dose is 6 to 10 mg ciprofloxacin/kg body weight intravenous every eight hours within a maximum of 400 mg ciprofloxacin per dose.
- Cystic fibrosis
  Clinical and pharmacokinetic data support the use of ciprofloxacin in pediatric cystic fibrosis patients (aged 5-17 years) with acute pulmonary exacerbation associated with P. aeruginosa infection, at a dose of 10mg ciprofloxacin/kg body weight intravenously 3 times daily (maximum daily dose 1200mg ciprofloxacin).
- Inhalational anthrax (post-exposure)
  10 mg intravenous/kg twice daily. The maximum of 400 mg intravenously per dose should not be exceeded (maximum daily dose of 800 mg).
  Drug administration should begin as soon as possible after suspected or confirmed exposure.

Geriatric patients (>65 years)
Elderly patients should receive a dose as low as possible depending on the severity of their illness and the creatinine clearance.

Patients with renal and hepatic impairment
Adults:
- Impaired renal function
  - Patients with creatinine clearance between 31 and 60 ml/min/1.73m² or serum creatinine concentration is between 1.4 and 1.9 mg/100 ml the maximum daily dose should be 800 mg for an intravenous regimen.
  - Patients with creatinine clearance less than 30 ml/min/1.73m² or serum creatinine concentration equal or higher than 2.0 mg/100 ml, the maximum daily dose should be 400 mg for an intravenous regimen.
- Impaired renal function and hemodialysis
  - Patients with creatinine clearance between 31 and 60 ml/min/1.73m² or serum creatinine concentration is between 1.4 and 1.9 mg/100 ml the maximum daily dose should be 800 mg for an intravenous regimen.
  - Patients with creatinine clearance less than 30 ml/min/1.73m² or serum creatinine concentration equal or higher than 2.0 mg/100 ml, the maximum daily dose should be 400 mg for an intravenous regimen on dialysis days after dialysis.
- Impaired renal function and continuous ambulatory peritoneal dialysis (CAPD)
  - Addition of ciprofloxacin infusion solution to the dialysate (intraperitoneal): 50 mg ciprofloxacin / liter dialysate administered 4 times a day every 6 hours.
- Impaired liver function
  - No dose adjustment is required.
- Impaired renal and liver function
  - Patients with creatinine clearance between 31 and 60 ml/min/1.73m² or serum creatinine concentration is between 1.4 and 1.9 mg/100 ml the maximum daily dose should be 800 mg for an intravenous regimen.
  - Patients with creatinine clearance less than 30 ml/min/1.73m² or serum creatinine concentration equal or higher than 2.0 mg/100 ml, the maximum daily dose should be 400 mg for an intravenous regimen.

Children:
Dosing in children with impaired renal and or hepatic function has not been studies.

METHOD OF ADMINISTRATION
Ciprofloxacin solution for infusion should be administered by intravenous infusion over a period of 60 minutes. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.
The ciprofloxacin infusion solution is compatible with physiological saline, Ringer solution and Ringer lactate solution, 5 % and 10 % glucose solutions, 10 % fructose solution, and 5 % glucose solution with 0.225 % NaCl or 0.45 % NaCl. When ciprofloxacin infusion solutions are mixed with compatible infusion solutions, for microbiological reasons and light sensitivity these solutions should be administered shortly after admixture.
Unless compatibility with other infusion solutions/medicinal products has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discoloration.
Incompatibility appears with all infusion solutions/medicinal products that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially on combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.9-4.5).

DURATION OF TREATMENT
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course. It is essential to continue therapy for at least 3 days after disappearance of the fever or of the clinical symptoms. Mean duration of treatment:

Adults
- 1 day for acute uncomplicated gonorrhoea and cystitis,
- up to 7 days for infections of the kidneys, urinary tract, and abdominal cavity,
- over the entire period of the neutropenic phase in patients with weakened body defences,
- a maximum of 2 months in osteomyelitis,
- and 7-14 days in all other infections.

In streptococcal infections the treatment must last at least 10 days because of the risk of late complications.

Infections caused by *Chlamydia* should also be treated for a minimum of 10 days.

Children (1-17 ages)
- Complicated urinary tract infections and pyelonephritis
  For complicate urinary tract infections or pyelonephritis due to Escherichia coli, the duration of treatment is 10 – 21 days.
- Cystic fibrosis
  For acute pulmonary exacerbation of cystic fibrosis associated with P. aeruginosa infection in pediatric patients (aged 5-17years), the duration of treatment is 10-14 days.

Inhalational anthrax (post-exposure) in adults and children
The total duration of treatment of inhalational anthrax (post-exposure) with ciprofloxacin (intravenous or oral) is 60 days.

4.3 CONTRAINDICATION
Hypersensitivity to ciprofloxacin or other quinolone or any of the excipients (see section "*List of excipients*").
Concurrent administration of ciprofloxacin and tizanidine is contraindicated (see section "*Interaction with other medicinal products and other forms of interaction*").

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Severe Infections and/or infections due to Gram-positive or anaerobic bacteria
For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, ciprofloxacin should be used in combination with an appropriate antibacterial agent.

Streptococcus pneumoniae infections
Ciprofloxacin is not recommended for treatment of pneumococcal infections due to limited efficacy against *Streptococcus pneumoniae*.

Genital tract infections
Genital tract infections may be caused by fluoroquinolone-resistant Neisseria gonorrhoeae isolates. In genital tract infections thought or known to be due to N. gonorrhoeae, it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

Cardiac disorders
Ciproxin is associated with cases of QT prolongation (see "*Undesirable effects*"). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using Ciproxin with concomitant drugs that can result in prolongation with the QT interval (e.g., class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see '*Interaction with other medicinal products and other forms of interaction*') or in patients with risk factors for QT prolongation or torsade de pointes (e.g., congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalemia or hypomagnesemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Children and adolescents (1-17 ages)
As with drugs in its class, ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. The analysis of available safety data from ciprofloxacin use in patients less than 18 years of age, the majority of whom had cystic fibrosis, did not disclose any evidence of drug-related cartilage or articular damage. The use of Ciproxin for indications other than the treatment of acute pulmonary exacerbation of cystic fibrosis caused by *Pseudomonas aeruginosa* infection (children aged 5 – 17 years), complicated urinary tract infections and pyelonephritis due to *Escherichia coli* (children aged 1 – 17 years), and for the use in inhalational anthrax (post-exposure) was not studied. For other indications clinical experience is limited.
For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate.

Hypersensitivity
In some instances, the hypersensitivity and allergic reactions may occur following a single dose(see '*Undesirable effects*'), a physician should be informed immediately. Anaphylactic/anaphylactoid reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration (see '*Undesirable effects*'). In these cases, Ciproxin has to be discontinued and medical treatment (e.g. treatment for shock) is required.

Gastrointestinal system
In the event of severe and persistent diarrhea during or after treatment, a physician must be consulted, since this symptom can hide a serious intestinal disease (life threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment. In such cases ciprofloxacin must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally, 4 x 250 mg/day). Medicinal products that inhibit peristalsis are contraindicated.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with Ciproxin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see '*Undesirable effects*').
There can be a temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with Ciproxin (see '*Undesirable effects*').

Musculoskeletal system
*** Ciprofloxacin should avoid to be used in patients with myasthenia gravis because the symptoms can be exacerbated. (Special warning announced by Department of Health)**
Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with Ciproxin, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of Ciproxin therapy. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids.
At any sign of tendinitis (e.g. painfull swelling, inflammation), a physician should be consulted and the antibiotic treatment be discontinued. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise (as the risk for tendon rupture might increase otherwise).Ciproxin should be used with caution in patients with a history of tendon disorders related to quinolone treatment.

Nervous system
Ciproxin, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. In epileptics and in patients who have suffered from previous central nervous system (CNS) disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible undesirable CNS effects. Cases of status epilepticus have been reported (see 'Undesirable effects'). If seizures occur, Ciproxin should be discontinued.
Psychiatric reactions may occurred even after the first administration of fluoroquinolones, including Ciproxin. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self- injurious behaviour, such as attempted or completed suicide (see 'Undesirable effects') . In the event that the patient develops any of these reactions, Ciproxin should be discontinued and appropriate measures instituted.
Cases of sensory or sensorimotor polyneuropathy resulting in paresthesias, hypoesthesias, dysesthesias, or weakness have been reported in patients receiving fluoroquinolones including Ciproxin. Patients under treatment with Ciproxin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see '*Undesirable effects*').

Skin and appendages
Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking Ciproxin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitation (i.e. sunburn-like skin reactions) occurs (see '*Undesirable effects*').

Cytochrome P450
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicinal products are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxantines, caffeine, duloxetine, ropinirole, clozapine, olanzapine). Increased plasma concentrations associated with drug-specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see section "*Interaction with other medicinal products and other forms of interaction*").

Injection site reaction
Local intravenous site reactions have been reported with the intravenous administration of Ciproxin (see '*Undesirable effects*'). These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Interaction with tests
Ciprofloxacin *in vitro* potency may interfere with the *Mycobacterium tuberculosis* culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Ciproxin.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Drugs known to prolong QT interval
Ciproxin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see 'Special warnings and precautions for use').

Probenecid
Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and Ciproxin increases the ciprofloxacin serum concentrations.

Tizanidine
In a clinical study in healthy subjects, there was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect (see '*Cytochrome P450*' in section '*Special warnings and precautions for use*'). Tizanidine containing medicinal products must not be administered together with Ciproxin (See "*Contraindications*").

Theophylline
Concurrent administration of ciprofloxacin and theophylline containing medicinal products can cause an undesirable increase in the serum theophylline concentration. This can lead to theophylline-induced undesirable effects; in very rare cases, these undesirable effects can be life threatening or fatal. If concurrent use of the two medicinal products is unavoidable, the serum theophylline concentration should therefore be checked and the theophylline dose appropriately reduced (see '*Cytochrome P450*' in section '*Special warnings and precautions for use*').

Other xanthine derivatives
On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported.

Phenytoin
Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving Ciproxin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related undesirable effects when Ciproxin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Ciproxin with phenytoin.

Methotrexate
Renal tubular transport of methotrexate may be inhibited by concomitant administration of Ciproxin, potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate - associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant Ciproxin therapy is indicated.

NASID
Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Cyclosporin
A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Vitamin K antagonists
Simultaneous administration of Ciproxin with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of Ciproxin with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Oral antidiabetic agents
Hypoglycemia has been reported when Ciprobay and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), were co-administered, presumably by intensifying the action of the oral antidiabetic agent (see '*Undesirable effects*').

Duloxetine
In clinical studies, it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration (see '*Cytochrome P450*' in section "*Special warnings and precautions for use*").

Ropinirole
It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60 and 84%, respectively. Monitoring ropinirole-related side effects dose adjustment as appropriate is recommended during and shortly after co-administration with Ciproxin (see '*Cytochrome P450*' in section "*Special warnings and precautions for use*").

Lidocaine
It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine
Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised (see 'Cytochrome P450' in section "*Special warnings and precautions for use*").

Sildenafil
C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, the dosage of sildenafil should be considered to halve when prescribing Ciproxin concomitantly with sildenafil.

4.6 PREGNANCY AND LACTATION
Pregnancy
The safety of ciprofloxacin in pregnant women has not been established.Animal studies do not indicate reproductive toxicity. Based on animal studies, it cannot be excluded that the drug could cause damage to articular cartilage in the immature fetal organism (see '*Preclinical safety data*'), therefore, the use of Ciproxin is not recommended during pregnancy.
Animal studies have not shown any evidence of teratogenic effects (malformations) (see '*Preclinical safety data*').

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, the use of Ciproxin is not recommended during breast-feeding (see "*Preclinical safety data*").

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Fluoroquinolones including ciprofloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (see "*Undesirable effects*"). This applies particularly in combination with alcohol.

4.8 UNDESIRABLE EFFECTS
Summary of the safety profile
Adverse drug reactions based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51621).

Tabulated list of adverse reactions
The frequencies of ADRs reported with Ciproxin are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as:
very common (≥ 1/10),
common (≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000),
very rare (< 1/10,000).

The ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)		
Blood and lymphatic system disorders		Eosinophilia	Leukopenia Anemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia, Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life threatening)	
Immune system disorders			Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction	
Metabolism and nutrition disorders		Decreased appetite and food intake	Hyperglycemia Hypoglycemia		
Psychiatric disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behavior, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behavior, such as suicidal ideations / thoughts and attempted or completed suicide)	
Nervous system disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial Hypertension (pseudotumor cerebri)	Peripheral neuropathy and polyneuropathy
Eye disorders			Visual disturbances	Visual color distortions	
Ear and labyrinth disorders			Tinnitus Hearing loss	Hearing impaired	
Cardiac disorders			Tachycardia		QT prolongation, ventricular arrhythmia, torsades de points *
Vascular disorders			Vasodilation Hypotension Syncope	Vasculitis	
Respiratory, thoracic and mediastinal disorders			Dyspnea (including asthmatic condition)		
Gastrointestinal disorders	Nausea Diarrhea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepato-biliary disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)	
Skin and subcutaneous tissue disorders		Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal, connective tissue and bone disorders		Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis	
Renal and urinary disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		
General disorders and administration site conditions		Unspecific pain Feeling unwell Fever	Edema Sweating (hyperhidrosis)	Gait disturbance	
Investigations		Increase in blood alkaline phosphatase	Abnormal prothrombin level abnormal Increased amylase		International normalized ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see "*Special warnings and precautions for use*").

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Edema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

< The MedDRA preferred term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 14.0 (except for 'Mycotic superinfections' and 'Unspecific pain').>

Additional information on special populations
Pediatric patients
One study conducted in children from 1-17 ages evaluated musculoskeletal adverse effects including arthralgia, abnormal gait, abnormal joint exam and so on. Within 6 weeks of treatment initiation, the rates of these events occurred in ciprofloxacin-treated group were higher than comparator-treated patients. (see "*Special warnings and precautions for use*").
The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see '*Special warnings and precautions for use*').

Overdose
Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated
Only a small quantity of ciprofloxacin (< 10 %) is eliminated by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Ciprofloxacin is a synthetic broad spectrum quinolone antibacteridal agent.

Mechanism of Action
Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of bacterial type II topoisomerases (DNA gyrase and topoisomerase IV), which are required for bacterial DNA replication, transcription, repair, and recombination.

Mechanism of Resistance
In vitro resistance to ciprofloxacin is commonly due to target site mutations in bacterial topoisomerases IV and DNA gyrase through multiple-step mutations. Single mutations may result in reduced susceptibility rather than clinical resistance, but multiple mutations generally result in clinical resistance to ciprofloxacin and cross-resistance across the quinolone class.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanism may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by the qnr gene has been reported.Resistance mechanisms that inactive penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines may not interfere with the antibacterial activity of ciprofloxacin. Organisms resistant to these drugs may be susceptible to ciprofloxacin.
The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

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

The bacterial genus and species listed below have been shown to commonly be susceptible to ciprofloxacin *in vitro*:

Aerobic Gram-positive Microorganisms
Bacillus anthracis
Staphylococcus aureus (methicillin-susceptible isolates)
Staphylococcus saprophyticus
Streptococcus pyogenes

Aerobic Gram-negative microorganisms

Aeromonas spp.	*Moraxella catarrhalis*
Brucella spp.	*Neisseria meningitidis*
Citrobacter koseri	*Pasteurella spp.*
Francisella tularensis	*Salmonella spp.**
Haemophilus ducreyi	*Shigella spp.*
Haemophilius influenzae	*Vibrio spp.*
Legionella spp.	*Yersinia pestis*

Anaerobic microorganisms
Mobiluncus

Other Microorganisms
Chlamydia trachomatis
Chlamydia pneumoniae
Mycoplasma hominis
Mycoplasma pneumoniae

The following microorganisms show varying degrees of susceptibility to ciprofloxacin: *Acinetobacter baumannii, Burkholderia cepacia, Campylobacter* spp.*, Citrobacter freudii, Enterococcus faecalis, Enterobacter aerogenes, Enterobacter clocae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Providencia* spp.*, Pseudomonas aeruginosa, Pseudomonas fluorescens, Serratia marcescens, Peptostreptococcus* spp.*, Propionibacterium acnes.*

The following microorganisms are considered inherently resistant to ciprofloxacin: *Staphylococcus aureus* (methicillin-resistant) and *Stenotrophomonas maltophilia, Actinomyces, Enteroccus faecium, Listeria monocytogenes, Mycoplasma genitalium, Ureaplasma urealitycum,* Anaerobic microorganisms (Excepted *Mobiluncus, Peptostreptococcus, Propionibacterium acnes*).

5.2 Pharmacokinetic properties
Absorption
Following an intravenous infusion of ciprofloaxcin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Distribution
The protein binding of ciprofloxacin is low (20 - 30%), and the substance is present in plasma largely in a non-ionized form. Ciprofloxacin can diffuse freely into the extravascular space. The large steady state distribution volume of 2 – 3 L/kg body weight shows that ciprofloxacin penetrates in tissues resulting in concentrations which clearly exceed the corresponding serum levels.

Metabolism
Small concentrations of four metabolites have been reported, and were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3 display *in vitro* antimicrobial activity comparable to, or inferior to that of nalidixic acid. M 4, with the smallest quantity, is largely equivalent to norfloxacin in terms of *in vitro* antimicrobial activity.

Elimination
Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, non-renally.

Children
In a study in children, C^{max} and AUC were not age-dependent. No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg/TID) was observed. In ten children with severe sepsis, less than 1 year of age, C_{max} was 6.1 mg/L (range 4.6 – 8.3 mg/L) after a 1-hour intravenous infusion at a dose level of 10 mg/kg; and 7.2 mg/L (range 4.7 – 11.8 mg/L) for children between 1 and 5 years of age. The AUC-values were 17.4 mg*h/L (range 11.8 – 32.0 mg*h/L) and 16.5 mg*h/L (range 11.0 – 23.8 mg*h/L) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population, pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4 – 5 hours and the bioavailability of the oral suspension approximately 60%.

5.3 PRECLINICAL SAFETY DATA
Acute toxicity
The acute toxicity of ciprofloxacin after oral administration can be classified as very low. Depending on the individual species, the LD50 after intravenous infusion is 125 – 290 mg/kg.

Chronic Toxicity
Chronic tolerability studies over 6 months
Oral administration: Doses up to and including 500 mg/kg and 30 mg/kg were tolerated without damage by rats and monkeys, respectively. Changes in the distal renal tubules were again observed in some monkeys in the highest-dose group (90 mg/kg).
Parenteral administration: In monkeys slightly elevated urea and creatinine concentrations and changes in the distal renal tubules were recorded in the highest-dose group (20 mg/kg).

Carcinogenicity
In carcinogenicity studies in mice (21 months) and rats (24 months) with doses up to approximately 1000 mg/kg body weight/day in mice and 125 mg/kg body weight/day in rats (increased to 250 mg/kg bw/day after 22 weeks), there was no evidence of a carcinogenic potential at any dose level.

Reproduction Toxicology
Fertility Studies in Rats
Fertility, the intrauterine and postnatal development of the young, and the fertility of F1 generation were not affected by ciprofloxacin.
Embryotoxicity Studies
These yielded no evidence of any embryotoxic or teratogenic action of ciprofloxacin.
Perinatal and Postnatal Development in Rats
No effects on the perinatal or postnatal development of the animals were detected. At the end of the rearing period histological investigations did not show any sign of articular damage in the young.

Mutagenicity
Eight in vitro mutagenictiy tests have been conducted with ciprofloxacin.
Although two of the eight *in vitro* assays (i.e. the Mouse Lymphona Cell Forward Mutation Assay and the Rat Hepatocyte Primary Culture DNA Repair Assay [LIDS]) were positive, all of the *in vivo* test systems covering all relevant endpoints gave negative results.

Articular Tolerability Studies
As it is also known for other gyrase inhibitors, ciprofloxacin causes damage to the large, weight-bearing joints in immature animals.
The extent of the cartilage damage varies according to age, species, and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs ciprofloxacin at high doses (1.3 to 3.5 times the therapeutic dose) caused articular changes after two weeks of treatment, which were still observed after five months. At therapeutic doses no effects were observed.

6. PHARMACEUTICAL PARTICULARS
List of excipients
Lactic acid,
Sodium chloride,
Hydrochloric acid concentrated,
Water for injections

Incompatibilities
Ciproxin solution for infusion (0.9% NaCl)is compatible with physiological saline, Ringer solution and Ringer lactate solution, 5% and 10% glucose solutions, 10% fructose solution, and 5% glucose solution with 0.225% NaCl or 0.45% NaCl. When Ciproxin solutions for infusion (0.9% NaCl) are mixed with compatible infusion solutions, for microbiological reasons and light sensitivity these solutions should be administered shortly after admixture.
Unless compatibility with other solutions for infusion /medicinal products has been confirmed, the solution for infusion must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discoloration.
Incompatibility appears with all solutions for infusion /medicinal products that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially on combination with solutions adjusted to an alkaline pH (pH of the Ciproxin solutions for infusion (0.9% NaCl: 3.9 – 4.5).

Special precautions for use
Protect from light. Do not refrigerate or freeze.

Since the infusion solution is photosensitive, the infusion bottles should be removed from the box only immediately before use. In daylight conditions complete efficacy is guaranteed for a period of 3 days.
For ease of use the infusion vial stopper should be penetrated in the central ring. Penetration of the outer ring may result in damage to the vial stopper.

Instructions for use/handling
At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature (15– 25 °C). It is therefore recommended not to store the infusion solution in a refrigerator.

Keep drugs out of reach of children.
Do not use after the expiry date.

Presentation
50 ml (100 mg), 100 ml (200 mg), 200 ml (400 mg) per vial

Bayer Pharma AG, D-51368 Leverkusen, Germany
Ciproxin inf. sol. 50ml/100mg, 100ml/200mg, 200ml/400mg / CCDS16 / TW07 / 122012