2019年03月制訂（第8版）

台灣第一三共

可樂必妥® 靜脈輸液5毫克/毫升

Cravit® IV Solution for Infusion 5mg/ml

衛署藥製字第057185號

依衛授食字第1081400661A號公告加刊以下資訊：
Levofloxacin可能與肢體障礙及潛在不可逆嚴重不良反應之發生相關，包括肌腱炎、肌腱斷裂、周邊神經炎及中樞神經系統作用。

1. 醫藥產品名稱

台灣第一三共
可樂必妥®靜脈輸液5毫克/毫升
Cravit® IV Solution for Infusion 5mg/ml

2. 定性與定量組成

包含250毫克levofloxacin的50毫升小瓶。
包含500毫克levofloxacin的100毫升小瓶。
包含750毫克levofloxacin的150毫升小瓶。
完整賦形劑清單請見第 6.1 節。

3. 藥物形式

注射液。
透明的黃綠色等張溶液，pH值為4.3至5.3，體積莫耳滲透濃度為282 - 322 mOsm/litre。

4. 臨床特性

4.1 治療適應症

治療成人因對levofloxacin有感受性的致病菌所引起之下列感染：
- 社區型肺炎
- 複雜性泌尿道感染(包括腎盂腎炎)
- 慢性細菌性前列腺炎
- 皮膚和軟組織感染

說明：開立Cravit®處方前，應考慮國家及／或當地適當使用fluoroquinolones抗生素之準則。

4.2 劑量與施用方法 依文獻記載

本藥限由醫師使用
Cravit®注射液每天經由靜脈緩慢注射一或兩次。劑量依據感染類型與嚴重性，及假定致病病原的敏感性而定。通常可以依據患者狀況，在幾天內由一開始的靜脈注射治療轉換為口服治療(Cravit®膜衣錠500毫克)。由於非腸道與口服形式具有生體等效性，可以使用相同的劑量。

治療持續時間
治療持續時間視病情而有差異。如同一般抗生素治療，患者復原或有證據顯示細菌根除後，應持續施用Cravit® (注射液或錠劑)至少48到72小時。

施用方法
Cravit®注射液僅適用於緩慢靜脈注射；每日施用一或兩次。250毫克的注射時間必須至少30分鐘，而500毫克Cravit®注射液至少為60分鐘(見第4.4節)。依據患者狀況，可以在一開始施用靜脈注射幾天後，轉換為口服。不相容性請見第6.2節，與其他注射液的相容性請見第6.6節。

劑量
建議施用下列劑量的Cravit®：
腎功能正常患者的使用劑量(肌酸酐清除率>50 mL/min)

適　應　症	每日給藥劑量(依據嚴重性)
社區型肺炎	每日兩次 500 毫克
複雜性泌尿道感染(包括腎盂腎炎)	每日一次 250 毫克[1]
慢性細菌性前列腺炎	每日一次 500 毫克
皮膚和軟組織感染	每日兩次 500 毫克

[1]嚴重感染案例應考慮增加劑量。

特殊族群
腎功能受損(肌酸酐清除率≤50 mL/min)

	給　藥　方　式		
	250 mg/24 h	500 mg/24 h	500 mg/12 h
肌酸酐清除率	首次劑量：250毫克	首次劑量：500毫克	首次劑量：500毫克
50-20 mL/min	之後：125 mg/24 h	之後：250 mg/24 h	之後：250 mg/12 h
19-10 mL/min	之後：125 mg/48 h	之後：125 mg/24 h	之後：125 mg/12 h
<10 mL/min (包含血液透析及腹膜透析)[1]	之後：125 mg/48 h	之後：125 mg/24 h	之後：125 mg/24 h

[1]血液透析或腹膜透析(CAPD)後不須使用後續劑量。

肝功能受損
不須調整劑量，因為levofloxacin並非由肝臟任何部位代謝，主要由腎臟排除。

年長者
年長患者不須調整劑量，只需考量腎功能(見第4.4節肌腱炎及肌腱破裂與 QT間隔延長)。

4.3 禁忌症 依文獻記載

Cravit®注射液不得用於：
- 對levofloxacin或任何其他Quinolone及列於第6.1節賦形劑過敏的患者，
- 癲癇患者，
- 患有施用fluoroquinolone有關的肌腱病變病史的患者，
- 懷孕期間，
- 哺乳女性。

4.4 特別警告與使用注意事項 依文獻記載

依衛授食字第1081400661A號公告加刊以下資訊：
過去使用quinolone或fluoroquinolone類藥品曾發生嚴重不良反應的病人，應避免使用本藥。
依衛授食字第1081400661A號公告加刊以下資訊：
流行病學研究報告顯示，使用fluoroquinolone類藥品可能增加主動脈瘤及主動脈剝離相關風險，尤其是老年人。
當病人有動脈瘤疾病之家族史，或經診斷已有主動脈瘤及/或主動脈剝離，或具有加重主動脈瘤及主動脈剝離之危險因子(如：Marfan syndrome、vascular Ehlers-Danlos syndrome、Takayasu arteritis、giant cell arteritis、Behcet's disease、高血壓、已知有動脈粥樣硬化)時，levofloxacin需經謹慎評估其效益及風險與其他治療方式後方得使用。建議病人如有突發性腹痛、胸或背痛，應立即就醫。
小兒患者的安全性資料及適合劑量尚未確立。
依部授食字第1051403279A號公告加刊以下資訊：
觀察到使用levofloxacin 兒童患者，比起未使用者更易發生肌肉骨骼疾病(關節痛，關節炎，肌腱和步態異常)之不良反應。
動物實驗中在未成年的大鼠和幼犬，給予口服和靜脈注射之levofloxacin 皆會導致骨軟骨病(osteochondrosis)增加，且於幼犬組織病理學檢查顯示，其承受重量的關節(weight-bearing joint)軟骨持續病變。其他氟　諾酮類藥物亦會造成未成年動物承受重量的關節軟骨病變及關節病等不良反應。
對甲氧苯青黴素(methicillin)具有抗藥性之金黃色葡萄球菌(S. *aureus*)極有可能對fluoroquinolone類抗生素(包括levofloxacin)具抗藥性。因此，除非實驗室培養已證實此菌株會受levofloxacin所抑制(而且常用以治療MRSA的抗菌藥物均不適用時)，否則一般不建議用levofloxacin來治療已知或懷疑可能是MRSA感染所引起的症狀。
*大腸桿菌*是尿道感染中最常見的病原體，其對fluoroquinolone類藥物的抗藥性在歐盟各國中並不一致；建議開藥時須考量當地*大腸桿菌*對fluoroquinolone類藥物的抗藥情形。

注射時間
250毫克Cravit®注射液的建議注射時間為至少30分鐘，而500毫克為至少60分鐘。已知使用ofloxacin時，注射期間可能會發展出心跳過快及暫時性血壓降低。在罕見情況下，由於血壓大幅降低，可能發生循環性虛脫。如果懷疑注射levofloxacin (ofloxacin的L異構物)期間血壓降低，必須立即暫停注射。

鈉含量
本藥品每50 ml劑量中含有7.8 mmol (181 mg)的鈉，每100 ml劑量中則含有15.8 mmol (363 mg)的鈉。需要控管鈉攝取量的患者，請注意以上說明。

肌腱炎及肌腱斷裂
依衛授食字第1081400661A號公告加刊以下資訊：
肌腱炎及肌腱斷裂(好發於阿基里斯腱)，有時為雙側，可能在開始使用levofloxacin的48小時內很快發生，也可能甚至在停藥數個月後才發生。老年人、腎功能不良、曾進行器官移植或同時併用皮質類固醇的病人會增加肌腱炎及肌腱斷裂的風險，故使用本藥應避免併用皮質類固醇。
當出現肌腱炎的初期徵兆(如疼痛腫脹、發炎)，應停用levofloxacin並考慮使用替代藥物。受到影響的肢體應加以適當的治療(如加以固定) (見第4.3及4.8節)。倘出現肌腱病變的徵兆應避免使用皮質類固醇。
罕見情況下可能會發生肌腱炎，並可能導致肌腱破裂，有時會兩者同時發生。在60歲以上的患者、每日劑量達到1000 mg的患者及使用皮質類固醇的患者身上，肌腱炎及肌腱破裂的風險會增加。若患者年紀較長，請根據其肌酸酐清除率來調整每日劑量(見第4.2節)。因此如果為這類患者開立levofloxacin處方，應密切觀察。如果發生肌腱炎症狀，所有患者均應諮詢醫師。

梭狀芽胞桿菌(Clostridium difficile)引起的疾病
Levofloxacin治療期間或之後(包含治療數週後)發生的下痢，尤其是嚴重、持續及／或出血，可能是梭狀芽胞桿菌引起的疾病症狀。梭狀芽胞桿菌引起的疾病症狀含輕微的到危及性命的，最嚴重的症狀是偽膜性大腸炎(pseudomembranous colitis) (見第4.8節)。因此病人在levofloxacin治療期間或之後發生嚴重的下痢症狀，須考慮是否與此相關。如果懷疑或確認發生梭狀芽胞桿菌引起的疾病，應立即停用levofloxacin注射液，並立即針對患者進行適當的治療。在這種臨床情況下，禁用抑制腸蠕動的藥物。
依衛授食字第1081400661A號公告加刊以下資訊：

中樞神經系統作用
精神相關不良反應
Levofloxacin可能增加精神相關不良反應，包括中毒性精神病、精神病反應進展至自殺意念/想法、幻覺或妄想；憂鬱或自殘行為如企圖自殺或完成自殺；焦慮、躁動或緊張；精神混亂、瞻妄、失去方向感或注意力無法集中；失眠或做惡夢；記憶力受損。這些反應可能發生在第一次投藥後。建議使用本藥之病人倘出現前述不良反應，應立即告知醫療人員，停用此藥並開始適當的治療。
如果要將levofloxacin用於精神患者，或具有精神病史的患者，應特別注意。
依衛授食字第1081400661A號公告加刊以下資訊：
中樞神經系統不良反應
Levofloxacin可能與增加癲癇(痙攣)風險、增加顱內壓(假性腦腫瘤)、頭暈和顫抖有關。此類藥物已知會誘發癲癇或降低癲癇閾值。曾有癲癇重積狀態的通報案例。應小心使用於癲癇病人及已知或疑似患有可能會誘發癲癇或降低癲癇閾值之中樞神經疾病(如嚴重腦動脈硬化、有痙攣病史、腦部血流減少、腦部結構改變或中風)，或具其他可能會誘發癲癇或降低癲癇閾值危險因子(如藥物、腎功能不全)的病人。如發生癲癇應停用本藥並開始適當的治療。
Levofloxacin和其他Quinolone類藥物一樣，禁用於具有癲癇病史的患者(見第4.3節)，且用於容易發生痙攣的患者時或併用含有降低降低大腦痙攣閾值的藥物(如茶鹼)的患者(見第4.5節)，應特別小心。抽搐發作(見第4.8節)時，應停用levofloxacin治療。

缺乏G-6-磷酸去氫酶的患者
患有潛在或實際葡萄糖-6-磷酸去氫酶活性缺失的患者，使用Quinolone抗細菌感染藥物治療時，可能會發生溶血反應，因此這些患者使用levofloxacin時應特別監測可能出現的溶血症狀。

腎臟受損患者
由於levofloxacin主要由腎臟排除，應調整腎臟受損患者的Cravit®劑量(見第4.2節)。

過敏反應
Levofloxacin可能導致嚴重，甚至致命的過敏反應(如，導致過敏性休克的血管性水腫)，有時在初次給藥後就會發生(見第4.8節)。患者應立即停止治療，並聯繫醫師或急診室醫師，醫師會進行適當的緊急醫療處置。

嚴重水皰反應
有患者通報使用levofloxacin後出現嚴重的皮膚水皰反應，例如史帝文斯強生症候群(Stevens-Johnson syndrome)或毒性表皮溶解症(見第4.8節)。當患者出現皮膚及/或黏膜反應時，建議患者須馬上告知醫師，再決定是否繼續用藥。

血醣異常
依衛授食字第1081400661A號公告加刊以下資訊：
Levofloxacin可能與血糖異常有關，包括有症狀的高血糖和低血糖，通常發生於同時使用口服降血糖藥物(如glyburide)或胰島素之糖尿病病人，建議針對這些病人要小心監控血糖值。
曾有嚴重低血糖導致昏迷或死亡的通報案例。如使用本藥之病人發生低血糖反應，應停用本藥並立即開始適當的治療。
用於這些糖尿病患者時，建議小心監測血醣。(見第4.8節)。

預防光過敏反應
曾有levofloxacin引發的光過敏反應(見第4.8節)的案件，建議患者在治療期間及治療後48小時，應儘量不要接觸強烈日光或人工紫外光(如，白熾燈或日光浴)，以避免發生光過敏反應。

使用維他命K拮抗劑治療的患者
由於使用levofloxacin治療的患者併用維他命K拮抗劑(如warfarin)時，可能會增加凝血檢測參數(PT/INR)及／或出血，同時施用這些藥物時，應進行凝血檢測(見第4.5節)。

QT間隔延長
將包含levofloxacin在內的fluoroquinolones用於已知有QT間隔延長風險因子的患者時，應特別注意。這些風險因子包含：
- 先天性QT症候群
- 併用已知會延長QT間隔的藥物(如，類別IA與III抗心律不整藥物，三環抗憂鬱藥物，巨環黴素，抗精神病藥物等)。
- 電解質失衡尚未回復(如，血鉀過低症，血鎂過低症)
- 心臟疾病(如心臟衰竭，心肌梗塞，心跳過慢)(見第4.2節年長，第4.5節，第4.8節，第4.9節)。
- 年長患者及對延長QTc間隔藥物敏感的女性，故這類患者在使用fluoroquinolones類藥物包括levofloxacin時，需小心服用

周邊神經病變
服用fluoroquinolones (包含levofloxacin)的患者曾發生過周邊感覺神經病變及週邊感覺運動神經病變，其發作可能非常迅速(見第4.8節)。如果患者發生神經病變症狀，應停用levofloxacin，以避免發展出不可逆病症。

肝膽管疾病
使用levofloxacin曾發生過肝臟壞死案例，甚至產生致死的肝衰竭，這些案例主要發生在患有潛在嚴重疾病的患者身上，如敗血症(見第4.8節)。如果發展出肝臟疾病徵兆與症狀，如食欲不振、黃疸、尿液暗沈、腹部搔癢或易痛感，應建議患者停止治療並聯繫其醫師。

重症肌無力的惡化
Fluoroquinolones類藥物包括levofloxacin，具有阻斷神經肌肉傳導作用，會使具有重症肌無力的患者肌肉無力的情形更加惡化。具有重症肌無力的患者服用fluoroquinolone類藥物所產生上市後嚴重的副作用包括死亡及需要呼吸支援系統。故具有重症肌無力病史的患者不建議使用levofloxacin。

視覺病變
若視力減弱或眼睛出現任何異常狀況，請立即洽詢眼科醫師(見第4.7及4.8節)。

重複感染
使用levofloxacin (尤其長時間使用)可能會導致抗藥性菌種過度孳生，若在治療期間出現重複感染現象，須採取適當措施。

干擾實驗室檢測結果
正接受levofloxacin治療的患者，其尿液鴉片類篩檢可能會出現偽陽性的結果，可能需要使用專一性更高的方法，確認鴉片篩檢呈現陽性的結果。
Levofloxacin可能會抑制結核分支桿菌(*Mycobacterium tuberculosis*)的生長，因此在進行結核病的細菌診斷時，可能會出現偽陰性的結果。

4.5 與其他醫藥產品的交互作用，及其他形式的交互作用 依文獻記載

其他醫藥產品對於Cravit®的影響
Theophylline、fenbufen或類似的非皮質類固醇抗發炎藥物
臨床研究中沒有發現到levofloxacin和theophylline會產生藥物動力學交互作用。不過quinolones與theophylline、非皮質類固醇發炎藥物、或降低痙攣閾值的藥物同時施用時，可能會導致大腦痙攣閾值大幅降低。在fenbufen存在的情況下，levofloxacin的濃度大約比單獨施用時高13%。
Probenecid與cimetidine
Probenecid與cimetidine在統計上會顯著影響levofloxacin的排除。Cimetidine與probenecid分別會降低levofloxacin的腎臟排除率24%與34%。這是因為這兩種藥物都能阻斷levofloxacin透過腎管分泌。不過，使用研究測試過的劑量時，統計上有顯著的動力學差異，但不太可能產生臨床上重要的影響。同時施用levofloxacin及影響腎管分泌的藥物，如probenecid與cimetidine時，應特別注意，尤其是用在腎臟受損的患者身上時。

其他重要資訊
臨床藥理學研究已經顯示，levofloxacin與下列藥物同時施用時，其藥物動力學不會受到臨床上重要的影響：碳酸鈣、毛地黃、glibenclamide、ranitidine。

Cravit®對於其他藥物的影響
Cyclosporin
Cyclosporin與levofloxacin同時施用時，半衰期會增加33%。
維他命K拮抗劑
併用levofloxacin與維他命K拮抗劑(如warfarin)的患者，曾發生凝血檢測參數(PT/INR)及／或出血增加的情況，這些情況可能很嚴重。因此，應密切監測使用維他命K拮抗劑治療患者的凝血參數(見第4.4節)。
已知延長QT間隔的藥物
Levofloxacin和其他fluoroquinolones一樣，用於服用已知延長QT間隔藥物的患者時，應特別小心(如，類IA及III抗心律不整藥物、三環抗憂鬱劑、巨環黴素、抗精神病藥物)。(見第4.4節QT間隔延長)。
其他相關資訊
在一項藥物動力學的交互作用實驗中，發現levofloxacin未影響theophylline (為CYP1A2的探針性受質)的藥物動力學，表示levofloxacin不是CYP1A2的抑制劑。

4.6 生育能力、懷孕與哺乳 依文獻記載

懷孕
關於懷孕婦女使用levofloxacin的資料，其數量相當有限，而動物實驗並沒有發現直接或間接的生殖毒性(見第5.3節)。不過在缺乏人類資料，且實驗室的資料說明fluoroquinolones具有破壞成長生物承重軟骨的風險，levofloxacin不應用於懷孕女性(見第4.3與5.3節)。

哺乳
Cravit®禁用於哺乳中的婦女。目前沒有足夠的資訊以了解levofloxacin是否會進入人類母乳中；不過其他fluoroquinolone類的藥物會進入母乳中。在缺乏人類資料，且fluoroquinolones具有破壞成長生物承重軟骨的可能實驗風險的情況下，levofloxacin不應用於哺乳女性(見第4.3與5.3節)。

生育能力
Levofloxacin不會損害大鼠的生育能力及生殖行為。

4.7 對於開車與操作機器能力的影響 依文獻記載

某些不良影響(如暈眩、嗜睡、視覺模糊)可能影響患者的集中力與反應能力，因此在這些能力特別重要的情況下，可能會造成風險(如，開車或操作機器)。

4.8 不良反應 依文獻記載

下列資訊來自超過8300位患者參與的臨床研究，及上市後的廣泛用藥經驗。表中列出的頻率定義如下：很常見(≥1/10)，常見(≥1/100, <1/10)，不常見(≥1/1000, <1/100)，罕見(≥1/10000, <1/1000)，很罕見(<1/10000)，未知(無法依據現有資料推估)。在每個頻率分群中，不良反應依據遞減的嚴重性排序。

系統器官類別	常見 (≥1/100，to <1/10)	不常見 (≥1/1000，to <1/100)	罕見 (≥1/10000， to <1/1000)	未知 (無法依據現有資料推估)
傳染與感染		真菌感染包括念珠菌感染及具抗藥性致病菌增生		
血液與淋巴系統疾病		白血球減少、嗜伊紅血球增加	血小板減少、嗜中性白血球減少	各類血細胞減少、顆粒性白血球缺乏症、溶血性貧血
免疫系統疾病			血管神經性水腫、過敏	過敏性休克(anaphylactic shock及anaphylactoid shock, 見第4.4節)[a]
代謝與營養疾病		食欲不振	血糖過低，尤其是糖尿病患者(見第4.4節)	高血糖、血糖過低引起的昏迷(見第4.4節)
精神疾病	失眠	焦慮、意識混淆、神經質	精神病反應(如幻覺、偏執行為)、憂鬱、易感易怒、異常多夢、作惡夢	具有自殘行為的精神病反應包含自殺念頭或行為(見第4.4節)
神經系統疾病	頭痛、暈眩	嗜睡、顫抖、味覺障礙	抽搐、感覺異常	周邊感覺神經病變(見第4.4節)、周邊感覺運動神經病變(見第4.4節)、味覺錯亂包括嗅覺喪失、運動障礙、錐體外障礙、味覺喪失、昏厥、良性的顱內高血壓
眼疾			視覺障礙如視覺模糊(見第4.4節)	暫時性地視覺喪失(見第4.4節)
耳朵與迷路病變		暈眩	耳鳴	聽力喪失、聽力受損
心臟疾病			心跳過快心悸	心室性心律過速所導致的心臟停、心室性心律不整及torsade de pointes (病人主要會發生延長QT間隔的危險性)、心電圖QT間隔延長(見第4.4節及4.9節)
血管疾病	限於靜脈注射劑型：靜脈炎		低血壓	
呼吸、胸部與縱膈疾病		呼吸困難		支氣管痙攣、過敏性肺炎
胃腸道疾病	下痢、嘔吐、噁心	腹部疼痛、消化不良、脹氣、便祕		出血性下痢，極罕見的案例顯示可能患有腸炎，包含偽膜性大腸炎(見第4.4節)、胰臟炎
肝膽管疾病	肝臟酵素增加(ALT/AST，鹼性磷酸酶，GGT)	血中膽紅素增加		黃疸與嚴重肝受損，包含急性肝衰竭，主要發生在患有嚴重潛在疾病的患者(見第4.4節)、肝炎
皮膚與皮下組織疾病[b]		出疹、搔癢症、蕁麻疹、多汗症		毒性表皮壞死、Stevens-Johnson症候群、多形性紅斑、光過敏反應(見第4.4節)、白血球破碎性血管炎、口腔炎
肌肉骨骼與結締組織疾病		關節痛、肌肉痛	肌腱病變包含肌腱炎(如，阿基里斯腱Achilles tendon)(見第4.3節及4.4節)、肌肉虛弱對患有重症肌無力的患者可能特別重要(見第4.4節)	橫紋肌溶解、肌腱破裂(如，阿基里斯腱Achilles tendon)(見第4.3節及4.4節)、韌帶破裂、肌斷裂關節炎
腎臟與尿道疾病		血中肌酸酐增加	急性腎衰竭(如，導因於間質性腎炎)	
一般疾病與施用部位症狀	限於靜脈注射劑型：注射部位反應(疼痛、發紅)	虛弱	發熱	疼痛(包含背部、胸腔及四肢疼痛)

[a] 過敏性與類過敏性反應有時可能在第一劑後就發生
[b] 黏膜皮膚反應有時候在第一劑後就會發生

其他與施用fluoroquinolones類藥物有關的不良作用包含：
- 紫質症患者紫質沈積發作。

4.9 劑量過量

依據超過治療劑量的動物研究或臨床藥理學研究，最重要的Cravit®注射液急性劑量過量徵兆為中樞神經系統症狀，例如精神混亂，暈眩，意識模糊，及抽搐性痙攣，QT間隔增加。
藥品上市後使用經驗，曾有患者出現中樞神經系統症狀，包括精神混亂、痙攣、幻覺以及打顫。
劑量過量時，應針對症狀進行治療。應進行心電圖監測，因為可能發生QT間隔延長。血液透析，包含腹部透析與 CAPD，不足以將levofloxacin從身體排除。目前沒有專用的解毒劑。

5. 藥理性質

5.1 藥物藥效學性質 依文獻記載

藥物治療分類：Quinolones類抗細菌感染藥物，fluoroquinolones ATC代碼：J01MA12
Levofloxacin是一類合成fluoroquinolones類抗細菌感染藥物，是左右旋混合藥物ofloxacin的S(-)對映異構體。

作用機制
作為一種fluoroquinolones類抗細菌感染藥物，levofloxacin作用在DNA-DNA-促旋酶(gyrase)複合體與第四型拓樸異構酶(topoisomerase IV)。

PK/PD關連性
Levofloxacin的殺菌活性，與血中最大濃度(C_{max})或曲線下面積(AUC)和最低抑制濃度(MIC)之間的比例有關。

抗藥性產生機制
菌種須經過一連串的過程才會對levofloxacin產生抗藥性，其過程須包括在第二型拓樸異構酶、DNA促旋酶以及拓樸異構酶IV的藥物作用點上發生突變。其他的抗藥機制，例如滲透性屏障(常見於綠膿桿菌)以及藥物排出機制，都有可能影響菌株對levofloxacin的抗藥性。
levofloxacin與其他fluoroquinolones之間有交叉抗藥性。基於其作用機制，levofloxacin與其他類別的抗細菌感染藥物之間，通常沒有交叉抗藥性。

用藥臨界點
EUCAST將levofloxacin易感與中度易感菌種分開，中度易感與抗藥性菌種分開，其建議之MIC用藥臨界點列在下面的MIC 檢測(mg/L)表中。

EUCAST的levofloxacin用藥臨床MIC臨界點(version 2.0, 2012-01-01)：

病原	易感性	抗藥性
腸桿菌 (Enterobacteriacae)	≦1 mg/L	＞2 mg/L
假單胞菌屬 (Pseudomonas spp.)	≦1 mg/L	＞2 mg/L
不動桿菌屬 (Acinetobacter spp.)	≦1 mg/L	＞2 mg/L
葡萄球菌屬 (Staphylococcus spp.)	≦1 mg/L	＞2 mg/L
肺炎鏈球菌 (S.pneumoniae)[1]	≦2 mg/L	＞2 mg/L
A,B,C,G型鏈球菌	≦1 mg/L	＞2 mg/L
感冒嗜血桿菌 (H.influenzae)[2, 3] 黏膜炎莫氏菌 (M.catarrhalis)[3]	≦1 mg/L	＞1 mg/L
與菌種無關之用藥臨界點[4]	≦1 mg/L	＞2 mg/L

1. Levofloxacin之用藥臨界點關係到高劑量療法中的劑量。
2. Fluoroquinolone也可能引起低程度的抗藥性(ciprofloxacin之MICs為0.12-0.5 mg/l)，不過目前沒有證據顯示此抗藥性在*感冒嗜血桿菌*引發的呼吸道感染中，具有任何臨床重要性。
3. MIC值高於易感臨界點的菌株非常罕見，或者尚未有報告證實。這些菌株分離出來之後的鑑定結果，及細菌對藥物的敏感性測試皆必須重複檢測，若結果確認無誤，必須將此分離出來的菌株送至評估中心(reference laboratory)；直到有臨床反應證實此菌株的MIC值高於目前的抗藥性臨界點，才可通報其抗藥情形。
4. 臨界值適用口服劑量為500 mg x 1至500 mg x 2，靜脈注射的劑量為500 mg x 1至500 mg x 2。

特定菌種不同地區時間的抗藥性發生率可能有差異，最好能取得當地抗藥性資訊，尤其是治療嚴重感染的時候。在當地抗藥性發生率達到將藥物用於至少某些類型感染的效果存疑時，應視需要尋求專家建議。

常見易感性菌種

好氧性革蘭氏陽性菌
炭疽桿菌(*Bacillus anthracis*)
甲氧苯青黴素(methicillin)有效之金黃色葡萄球菌
腐生性葡萄球菌(Staphylococcus saprophyticus)
C型及G型鏈球菌
無乳鏈球菌(Streptococcus agalactiae)
肺炎鏈球菌
化膿性鏈球菌(Streptococcus pyogenes)

好氧性革蘭氏陰性菌
嚙蝕艾肯氏菌(Eikenella corrodens)
感冒嗜血桿菌(Haemophilus influenzae)
副流感嗜血桿菌(Haemophilus para-influenzae)
產酸克雷伯氏菌(Klebsiella oxytoca)
Moraxella catarrhalis
巴斯德桿菌(Pasteurella multocida)
普通變形桿菌(Proteus vulgaris)
Providencia rettgeri

厭氧菌
消化鏈球菌屬(Peptostreptococcus)

其他
肺炎披衣菌(Chlamydophila pneumoniae)
鸚鵡熱披衣菌(Chlamydophila psittaci)
砂眼披衣菌(Chlamydia trachomatis)
肺炎退伍軍人桿菌(Legionella pneumophila)
肺炎黴漿菌(Mycoplasma pneumoniae)
人型黴漿菌(Mycoplasma hominis)
尿溶性尿漿菌 (Ureaplasma urealyticum)

獲得抗藥性後可能造成問題的菌種

好氧性革蘭氏陽性菌
糞腸球菌 (Enterococcus faecalis)
具甲氧苯青黴素抗藥性之金黃色葡萄球菌#
凝血酶陰性之葡萄球菌屬

好氧性革蘭氏陰性菌
鮑氏不動桿菌 (Acinetobacter baumannii)
弗氏檸檬酸菌 (Citrobacter freundii)
產氣桿菌 (Enterobacter aerogenes)
陰溝腸桿菌 (Enterobacter cloacae)
大腸桿菌 (Escherichia coli)
Morganella morganii
肺炎克雷伯氏菌 (Klebsiella pneumonia)
奇異變形桿菌 (Proteus mirabilis)
Providencia stuartii
綠膿桿菌 (Pseudomonas aeruginosa)
沙雷氏黏質菌 (Serratia marcescens)

厭氧菌
鬆脆桿菌 (Bacteroides fragilis)

本質抗藥性菌種 (Inherently resistant strains)

好氧性革蘭氏陽性菌
Enterococcus faecium
#對甲氧苯青黴素(methicillin)具有抗藥性之金黃色葡萄球菌(S. *aureus*)極有可能對fluoroquinolone類抗生素(包括levofloxacin)也具抗藥性。

5.2 藥物動力學性質 依文獻記載

吸收
口服施用levofloxacin會迅速並幾乎完全吸收，1-2小時內達到最高血中濃度。絕對生體可用率為99-100%。
食物對levofloxacin吸收的影響很小。
每日給予500 mg藥物一次或兩次之後，在48小時之內可達到穩定狀態。

分佈
大約30-40%的levofloxacin與血中蛋白質結合。毫克毫克在單劑及重複給予500 mg的levofloxacin之後，其平均分佈體積為100公升，表示藥物廣泛散佈於身體組織中。

穿透進入組織與體液：
已知levofloxacin可穿透進入支氣管黏膜、上皮內襯液體、肺泡巨噬細胞、肺組織、皮膚(水皰中的液體)、前列腺組織以及尿液，不過levofloxacin穿透到腦脊髓液的能力很差。

生體轉換
Levofloxacin 被代謝的比例很低，代謝物為desmethyl - levofloxacin 與levofloxacin N-oxide。這些代謝物佔尿液排出劑量的5%以下。Levofloxacin的立體化學性質穩定，不會進行鏡像異構物轉換。

排除
口服與靜脈施用levofloxacin後，會以相對較慢的速率從血中排出($t_{1/2}$：6-8小時)。主要經由腎臟途徑排除(>85%的施用劑量)。
單劑量500 mg的levofloxacin，其平均全身清除率為175 +/-29.2 ml/min。
靜脈注射與口服施用levofloxacin後，藥物動力學沒有重大差異，顯示口服與靜脈注射給藥方式可以互換。

線性
Levofloxacin在50到1000毫克劑量範圍內，遵循線性藥物動力學。

特殊族群

腎功能不全患者
Levofloxacin的藥物動力學可能會受到腎功能不全的影響。腎功能下降時，腎臟的排出與清除量會下降，而排除半衰期會如下表所示增加：
單劑量口服500 mg後腎功能不足患者之藥物動力學

Cl_{cr} [mL/min]	<20	20-49	50-80
Cl_R [mL/min]	13	26	57
$t_{1/2}$ [小時]	35	27	9

年長患者
年輕與年長受試者的levofloxacin藥物動力學沒有顯著差異，與肌酸酐清除率有關的參數除外。

性別差異
男性與女性受試者的獨立分析顯示，levofloxacin藥物動力學有很小到最低限度的性別差異。沒有證據顯示這些性別差異在臨床上有任何重要性。

5.3 臨床前安全性資料 依文獻記載

非臨床資料顯示levofloxacin對人體不會產生特殊傷害，此資料是根據一般執行的單劑量毒性試驗、重複劑量毒性試驗、致癌風險以及對生殖與發育的毒性試驗所得出的結果。
Levofloxacin不會損害大鼠的生育能力及生殖行為；由於母體毒性，levofloxacin對胚胎的唯一影響為生長遲緩。
在活體外實驗中，levofloxacin不會誘發細菌或哺乳動物細胞的基因突變，不過會誘發中國倉鼠肺細胞的染色體異常；這些現象可歸因於levofloxacin抑制了第二型拓樸異構酶。在體內實驗中(微核、姐妹分體交換、未排定DNA合成試驗、顯性致死試驗)，未顯示levofloxacin具有任何基因毒性的可能性。
小鼠研究顯示，levofloxacin只會在很高劑量具有光毒性活性。levofloxacin在光致突變檢測中，沒有觀察到任何基因毒性，且在光致癌性檢測中，減緩腫瘤的發展。

6. 藥物細目

6.1 賦形劑清單

氯化鈉
氫氧化鈉(調節pH值)
鹽酸(調節pH值)
注射用水

6.2 不相容性

Cravit® 5 mg/mL注射液不應與肝素或鹼性溶液混合(如碳酸氫鈉) 。
除了第6.6節所列產品外，本藥品不得與其他藥品混合。

6.3 保存期限

如外包裝所示
移除外包裝後保存期限：3天(室內照明下)。
橡膠塞子穿孔後保存期限：立即使用(見第6.6節)。
從微生物學觀點來看，注射液應立即使用。如果沒有立即使用，使用中儲存時間與條件為使用者應承擔之責任。

6.4 儲存特殊注意事項

將瓶子放在外盒中，以防止光照(見第6.3節)。使用前先檢查外觀。只應使用不含顆粒的清澈溶液。
30°C以下貯存。

6.5 容器本質與內容物

具有鋁質封膜、氯化丁基橡膠塞及可撕開聚丙烯蓋的50毫升第I型玻璃小瓶。每瓶包含50毫升注射液。
具有鋁質封膜、氯化丁基橡膠塞及可撕開聚丙烯蓋的100毫升第I型玻璃小瓶。每瓶包含100毫升注射液。
具有鋁質封膜、氯化丁基橡膠塞及可撕開聚丙烯蓋的150毫升第I型玻璃小瓶。每瓶包含150毫升注射液。

6.6 棄置特殊注意事項

Cravit®注射液應在橡膠塞子穿孔後立即使用(3小時內)，以避免任何細菌污染。注射時不須避免光照。
如同所有藥物，任何未使用的藥品應依據並符合當地環保法規棄置。
本藥物包裝僅限單次使用。
使用前請以目測檢查溶液狀態，當溶液為透明黃綠色且不含任何雜質時，方可使用。

與其他注射液混合使用：
Cravit®注射液與下列注射液相容：
0.9 %氯化鈉濃液USP。
5%葡萄糖注射液USP。
含2.5%葡萄糖的林格氏液。
與非腸道營養劑併用(胺基酸，葡萄糖，電解質)。
不相容性請參見第6.2節。

台灣第一三共股份有限公司
Daiichi-Sankyo
製造廠：健亞生物科技股份有限公司
新竹縣湖口鄉新竹工業區工業一路1號
委託者：台灣第一三共股份有限公司
台北市八德路二段308號7樓之1
電話：(02)8772-2250

DSTW201903-04

Cravit IV Solution for Infusion 5mg/ml

According to MOHW's official letter (衛授食字第1081400661A公告), the following wording has been added:
Levofloxacin have been associated with disabling and potentially irreversible serious adverse reactions, including tendinitis, tendon rupture, peripheral neuropathy and central nervous system effects.

1 NAME OF THE MEDICINAL PRODUCT
Cravit 5 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
250 mg of levofloxacin in a 50 ml glass bottle
500 mg of levofloxacin in a 100 ml glass bottle
One ml of solution for infusion contains 5 mg of levofloxacin
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Solution for infusion.
Clear greenish-yellow solution with pH of 4.3 to 5.3 and osmolarity of 282-322 mOsm/litre.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
In adults for whom intravenous therapy is considered to be appropriate, Cravit solution for infusion is indicated for the treatment of the following infections when due to levofloxacin susceptible microorganisms:
- Community-acquired pneumonia.
- Complicated urinary tract infections including pyelonephritis.
- Chronic bacterial prostatitis.
- Skin and soft tissue infections.

Before prescribing Cravit, consideration should be given to national and/or local guidance on the appropriate use of fluoroquinolones.

4.2 Posology and method of administration
Cravit solution for infusion is administered by slow intravenous infusion once or twice daily. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen. It is usually possible to switch from initial intravenous treatment to the oral route after a few days (Cravit 250 or 500 mg tablets), according to the condition of the patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Duration of treatment
The duration of treatment varies according to the course of the disease. As with antibiotic therapy in general, administration of Cravit (solution for infusion or tablets) should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Method of administration
Cravit solution for infusion is only intended for slow intravenous infusion; it is administered once or twice daily. The infusion time must be at least 30 minutes for 250 mg or 60 minutes for 500 mg Cravit solution for infusion (see section 4.4). It is possible to switch from an initial intravenous application to the oral route at the same dosage after a few days, according to the condition of the patient.
For incompatibilities see section 6.2 and compatibility with other infusion solutions see section 6.6.

Posology
The following dose recommendations can be given for Cravit:
Dosage in patients with normal renal function (creatinine clearance > 50 ml/min)

Indication	Daily dose regimen (according to severity)
Community-acquired pneumonia	500 mg twice daily
Complicated urinary tract infections including pyelonephritis	250 mg[1] once daily
Chronic bacterial prostatitis.	500 mg once daily
Skin and soft tissue infections	500 mg twice daily

[1] Consideration should be given to increasing the dose in cases of severe infection.

Special populations
Impaired renal function (creatinine clearance ≤ 50 ml/min)

	Dose regimen		
	250 mg/24 h	500 mg/24 h	500 mg/ 12h
Creatinine clearance	first dose: 250 mg	first dose: 500 mg	first dose: 500 mg
50 - 20 ml/min	then: 125 mg/24 h	then: 250 mg/24 h	then: 250 mg/12 h
19-10 ml/min	then: 125 mg/48 h	then: 125 mg/24 h	then: 125 mg/12 h
< 10 ml/min (including haemodialysis and CAPD)[1]	then: 125 mg/48 h	then: 125 mg/24 h	then: 125 mg/24 h

[1] No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Impaired liver function
No adjustment of dosage is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

In the elderly
No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function (See section 4.4 "Tendinitis and tendon rupture" and "QT interval prolongation").

4.3 Contraindications
Cravit solution for infusion must not be used:
- in patients hypersensitive to levofloxacin or any other quinolone and any of the excipients listed in section 6.1,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- during pregnancy,
- in breast-feeding women.

4.4 Special warnings and precautions for use
According to MOHW's official letter (衛授食字第1081400661A 公告), the following wording has been added:
Avoid the use of quinolones and fluoroquinolones in patients who experience any of these serious adverse reactions.
According to MOHW's official letter (衛授食字第1081400661A 公告), the following wording has been added:
Epidemiological studies have shown that the use of fluoroquinolones may increase the related risk of aortic aneurysm and aortic dissection, especially in the elderly.
When the patient has a family history of aneurysm disease, or has been diagnosed with aortic aneurysm and/or aortic dissection, or has a risk factor for aggravating aortic aneurysm and aortic dissection (eg, Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, and known atherosclerosis), levofloxacin need to be carefully evaluated for their benefits and risks with other treatments. Patients are advised to seek immediate medical attention if they have sudden abdominal pain, chest or back pain.
Safety and suitable posology in pediatric patients have not been established.
According to TFDA's official letter (部授食字第1051403279A 公告), the following wording has been added:
The adverse event was observed: the child patient use levofloxacin are easier occur the Musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) that compared to not used patient. In animal study of immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased osteochondrosis, and histopathological examination indicates cartilage of weight-bearing joint persistently lesions. Other fluoroquinolones also produce the adverse event of cartilage of weight-bearing joints lesion and other arthropathy in immature animals.
Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).
Resistance to fluoroquinolones of *E. coli* – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *E. coli* to fluoroquinolones.

Infusion Time
The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500mg Cravit solution for infusion should be observed. It is known for ofloxacin, that during infusion tachycardia and a temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur.
Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, (l-isomer of ofloxacin) the infusion must be halted immediately.

Sodium content
This medicinal product contains 7.8 mmol (181 mg) sodium per 50 ml dose and 15.8 mmol (363 mg) per 100 ml dose. To be taken into consideration by patients on a controlled sodium diet.

Tendinitis and tendon rupture
According to MOHW's official letter (衛授食字第1081400661A 公告), the following wording has been added:
Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur very quickly within 48 hours of starting fluoroquinolone drugs, or even several months after discontinuation of the drug. Elderly patients, renal dysfunction, patients who have undergone organ transplantation, or combined use of corticosteroids may increase the risk of tendinitis and tendon rupture, so the use of this drug should be avoided to combine corticosteroids.
When initial signs of tendonitis (such as swelling, inflammation) occur, levofloxacin should be discontinued and considered alternative drugs. The affected limb should be treated appropriately (such as immobilisation). Corticosteroids should be avoided if signs of tendonopathy occur.
Tendinitis may rarely occur and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased patients aged over 60 years, in patients receiving daily doses of 1000mg and in patients using corticosteroids. The daily dose should be adjusted in elderly patients based on creatinine learance (see section 4.2). Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis.

Clostridium difficile-associated disease
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin (including several weeks after treatment), may be symptomatic of Clostridium difficile-associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, levofloxacin should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal productsare contraindicated in this clinical situation.
According to MOHW's official letter (衛授食字第1081400661A 公告), the following wording has been added:

Central nervous system effects
Psychiatric Adverse Reactions
Levofloxacin have been associated with an increased of psychiatric adverse reactions, including: toxic psychoses, psychotic reaction progresses to suicidal idea/thoughts, hallucinations or delusion; depression or self-harm is an attempt to commit suicide or complete suicide; anxiety, agitation or nervousness; confusion, delirium, disorientation or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. If these adverse reactions occur in patients receiving this drug, recommend to inform health professional immediately, discontinue this drug and institute appropriate measures.
Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.
According to MOHW's official letter (衛授食字第1081400661A 公告), the following wording has been added:
Central Nervous System Adverse Reactions
Levofloxacin have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (pseudotumor cerebri), dizziness, and tremors. This kind of drugs may predispose them to seizures or lower the seizure threshold. Status epilepticus have been reported. Care should be taken in patients with epilepsy and known or suspected to have central nervous system disorders that may predispose them to seizures or lower the seizure threshold. (e.g., severe cerebral arteriosclerosis, medical history of epilepsy, reducing blood flow of the brain, brain structural changes or stroke) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., drug, renal dysfunction). If epilepsy occur in patients, discontinue this drug and institute appropriate measures.
Levofloxacin is contraindicated in patients with a history of epilepsy (see section 4.3) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with drugs that lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures (see section 4.8), treatment with levofloxacin should be discontinued.

Patients with G-6- phosphate dehydrogenase deficiency
Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment
Since levofloxacin is excreted mainly by the kidneys, the dose of Cravit should be adjusted in patients with renal impairment (see section 4.2).

Hypersensitivity reactions
Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe bullous reactions
Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycaemia
According to MOHW's official letter (衛授食字第1081400661A 公告), the following wording has been added:
Levofloxacin have been associated with abnormal blood glucose, including symptomatic hyperglycemia and hypoglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended.
Severe cases of hypoglycemia resulting in coma or death have been reported. If a hypoglycemic reaction occurs in a patient being treated with this drug, discontinue this drug and initiate appropriate therapy immediately.
In these diabetic patients, careful monitoring of blood glucose is recommended. (See section 4.8).

Prevention of photosensitisation
Photosensitisation has been reported with levofloxacin (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists
Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomittantly (see section 4.5).

QT interval prolongation
Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations. (See section 4.2 Elderly, section 4.5, section 4.8, section 4.9).

Peripheral neuropathy
Peripheral sensory neuropathy and peripheral sensory motor neuropathy neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset (see section 4.8). Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Hepatobiliary disorders
Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis
Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Superinfection
The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Interference with laboratory test
In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.
Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal products and other forms of interaction
Effect of other medicinal products on Cravit
Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.
Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.
Probenecid and cimetidine
Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.
Caution should be exercised when levofloxacin is coadministered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information
Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of Cravit on other medicinal products
Cyclosporin
The half-life of cyclosporin was increased by 33% when coadministered with levofloxacin.
Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists (see section 4.4)
Drugs known to prolong QT interval
Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)). (See section 4.4 QT interval prolongation).

Other relevant information
In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). However in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weightbearing cartilage of the growing organism, levofloxacin must not be used in pregnant women (see sections 4.3 and 5.3).

Breast-feeding
Cravit solution for infusion is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women (see sections 4.3 and 5.3).

Fertility
Levofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on ability to drive and use machines
Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable effects
The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.
Frequencies in this table are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Common (≥1/100, to <1/10)	Uncommon (≥1/1000, to <1/100)	Rare (≥1/10000, to <1/1000)	not known (cannot be estimated from the available data)
Infections and infestations		Fungal infection including Candida infection Pathogen resistance		
Blood and the lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity (see section 4.4)	Anaphylactic shock[a] Anaphylactoid shock[a] (see section 4.4)
Metabolism and nutrition disorders		Anorexia	Hypoglycemia particularly in diabetic patients (see section 4.4)	Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4)
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion (see section 4.3 and 4.4) Paraesthesia	Peripheral sensory neuropathy (see section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders			Visual disturbances such as blurred vision (see section 4.4)	Transient vision loss (see section 4.4)
Ear and Labyrinth disorders		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac disorders			Tachycardia, Palpitation	Ventricular tachycardia which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see section 4.4 and 4.9)
Vascular disorders	Applies to iv form only: Phlebitis		Hypotension	
Respiratory, thoracic and mediastinal disorders		dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea- haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including fatal cases with acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Skin and subcutaneous tissue disorders[b]		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and Connective tissue disorders		Arthralgia Myalgia	Tendon disorders (see section 4.3 and 4.4) including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4)	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see section 4.3 and 4.4) Ligament rupture Muscle rupture Arthritis
Renal and urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to nephritis interstitial)	
General disorders and administration site conditions	Applies to iv form only: Infusion site reaction (pain、reddening)	Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

[a] Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose.
[b] Mucocutaneous reactions may sometimes occur even after the first dose

Other undesirable effects which have been associated with fluoroquinolone administration include:
- attacks of porphyria in patients with porphyria.

4.9 Overdose
According to toxicity studies in animals or clinical pharmacology studies performed with supratherapeutic doses, the most important signs to be expected following acute overdoseof Cravit solution for infusion are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval.
CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.
In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones
ATC code: J01MA12
Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic active substance ofloxacin.

Mechanism of action
As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

PK/PD relationship
The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (C_{max}) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance
Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also affect susceptibility to levofloxacin.
Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Breakpoints
The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).

EUCAST clinical MIC breakpoints for levofloxacin (version 2.0, 2012-01-01):

Pathogen Susceptible Resistant	Susceptible	Resistant
Enterobacteriacae	≤ 1 mg/L	> 2 mg/L
Pseudomonas spp.	≤ 1 mg/L	> 2 mg/L
Acinetobacter spp.	≤ 1 mg/L	> 2 mg/L
Staphylococcus spp.	≤ 1 mg/L	> 2 mg/L
S.pneumoniae[1]	≤ 2 mg/L	> 2 mg/L
Streptococcus A,B,C,G	≤ 1 mg/L	> 2 mg/L
H.influenzae[2, 3] M.catarrhalis[3]	≤ 1 mg/L	> 1 mg/L
Non-species related breakpoints[4]	≤ 1 mg/L	> 2 mg/L

1. The breakpoints for levofloxacin relate to high dose therapy.
2. Low-level fluoroquinolone resistance (ciprofloxacin MICs of 0.12-0.5 mg/l) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with *H. influenzae*.
3. Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
4. Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.

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

Commonly susceptible species

Aerobic Gram-positive bacteria
Bacillus anthracis
Staphylococcus aureus methicillin-susceptible
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus pyogenes
Streptococci, group C and G
Streptococcus pneumoniae

Aerobic Gram- negative bacteria
Haemophilus influenzae
Klebsiella oxytoca
Moraxella catarrhalis
Proteus vulgaris
Eikenella corrodens
Haemophilus para-influenzae
Pasteurella multocida
Providencia rettgeri

Anaerobic bacteria
Peptostreptococcus

Other
Chlamydophila pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae
Ureaplasma urealyticum
Chlamydophila psittaci
Mycoplasma hominis

Species for which acquired resistance may be a problem
Aerobic Gram-Positive bacteria
Enterococcus faecalis
Coagulase negative Staphylococcus spp
Staphylococcus aureus methicillin-resistant#
Aerobic Gram- negative bacteria
Acinetobacter baumannii
Enterobacter aerogenes
Enterobacter cloacae
Morganella morganii
Providencia stuartii
Serratia marcescens
Citrobacter freundii
Escherichia coli
Proteus mirabilis
Pseudomonas aeruginosa
Klebsiella pneumoniae

Anaerobic bacteria
Bacteroides fragilis

Inherently Resistant Strains
Aerobic Gram-positive bacteria
Enterococcus faecium
Methicillin-resistant S. aureus are very likely to possess co-resistance to fluoroquinolones, including levofloxacin.

5.2 Pharmacokinetic properties
Absorption
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 h. The absolute bioavailability is 99-100%.
Food has little effect on the absorption of levofloxacin.
Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

Distribution
Approximately 30 - 40 % of levofloxacin is bound to serum protein.
The mean volume of distribution of levofloxacin is approximately 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues.
Penetration into tissues and body fluids:
Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration intro cerebro-spinal fluid.

Biotransformation
Levofloxacin is metabolised to a very small extent, the metabolites being desmethyllevofloxacin and levofloxacin N-oxide. These metabolites account for < 5 % of the dose and are excreted in urine.
Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination
Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma ($t_{1/2}$: 6 - 8 h). Excretion is primarily by the renal route (> 85 % of the administered dose).
The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/-29.2 ml/min.
There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity
Levofloxacin obeys linear pharmacokinetics over a range of 50 to1000 mg.

Special populations
Subjects with renal insufficiency
The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below:
Pharmacokinetics in renal insufficiency following single oral 500 mg dose

Cl_{cr} [mL/min]	<20	20-49	50-80
Cl_R [mL/min]	13	26	57
$t_{1/2}$ [h]	35	27	9

Elderly subjects
There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

Gender differences
Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.
Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity.
Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells *in vitro*. These effects can be attributed to inhibition of topoisomerase II. *In vivo* tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.
Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photocarcinogenicity assay.
In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities
Cravit 5 mg/ml solution for infusion should not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate).
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
3 years
Shelf life after removal of the outer packaging: 3 days (under indoor light conditions).
Shelf life after perforation of the rubber stopper: immediate use (see section 6.6).
From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
Keep the bottle in the outer carton in order to protect from light (see section 6.3).
Inspect visually prior to use. Only clear solutions without particles should be used.

6.5 Nature and contents of container
50 ml type I glass bottle with flanged aluminium cap, chlorobutyl rubber stopper and tear-off polypropylene lid. Each bottle contains 50 ml solution for infusion. Pack sizes of 1 and 5 bottles.
100ml type I glass bottle with flanged aluminium cap, chlorobutyl rubber stopper and tear-off polypropylene lid. Each bottle contains 100 ml solution for infusion. Pack sizes of 1, 5 and 20 bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Cravit solution for infusion should be used immediately (within 3 hours) after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion.
The medicinal product is for single use only.
The solution should be visually inspected prior to use. It must only be used if the solution is clear, greenish-yellow solution, practically free from particles.
As for all medicines, any unused medicinal product should be disposed of accordingly and in compliance with local environmental regulations.

Mixture with other solutions for infusion:
Cravit solution for infusion is compatible with the following solutions for infusion:
0.9 % sodium chloride solution USP.
5 % glucose injection USP
2.5 % glucose in Ringer solution.
Combination solutions for parenteral nutrition (amino acids, glucose, electrolytes).
See section 6.2 for incompatibilities.

Manufactured by Genovate Biotechnology Co., Ltd No.1, First Industrial Rd., HsinChu Expanded Industrial Park, Taiwan R.O.C.