

Ciprofloxacin - MCC Standardised Package Insert vs Originator and International References

	Standardised PI	ok Ciprobay	ok USA/FDA	ok EMA	ok Canada	ok TGA	
1. INDICATIONS							Indications
Lower respiratory tract infections caused by : Ent. cloacae, E. coli, H. influenzae, H. parainfluenzae, Kl. pneumoniae, Pr. mirabilis, Ps. aeruginosa	x	x	x	x	x	x	Mean of p values=Overall p value 1.00+1.00+1.00+1.00+1.00+5=1.00
Urinary tract infections caused by : C. diversus, C. freundii, Ent.cloacae, E. coli, Kl. pneumoniae, M. morganii, P. mirabilis, Pr. rettgeri, Ps. aeruginosa, S. marcescens, S. epidermidis, S. faecalis	x	x	x	x	x	x	q=1.0-1.0=0.00
Skin and soft tissue infections caused by :C. freundii, Ent. cloacae, E. coli, Kl. pneumoniae, M. morganii, P. mirabilis, P. vulgaris, Pr. stuartii, Ps. aeruginosa, S. aureus, S. epidermidis, S. pyogenes	x	x	x	x	x	x	Std Deviation= $\sqrt{(pq+n)}=\sqrt{(0.0+5)}=\sqrt{0.0}=0.0$
Gastro-intestinal infections: Infective diarrhoea caused by C. jejuni, E. coli, S. flexneri, Sh. sonnei	x	x	x	x	x	x	95% CI = $p \pm (2.776 \times \text{Std Dev}) = p \pm (2.776 \times 0.00) = 0.00$
Bone infections : Osteomyelitis due to susceptible Gram-negative organisms	x	x	x	x	x	x	95%CI = 1.0±0.0 ie. 1.00 to 1.00
Gonorrhoea	x	x	x	x	x	x	
Total	6	6	6	6	6	6	
p= proportion		p=6/6=100	p=6/6=100	p=6/6=100	p=6/6=100	p=6/6=100	
2. RECOMMENDED DOSAGE							Dosage
Treatment of Ps. aeruginosa infections, aminoglycoside to be administered concomitantly	x	N	N	N	N	N	
Swallow whole with plenty of liquid	x	x	N	x	x	N	
Take with or without meals	x	x	N	x	x	N	
Dosage range 250 - 750 mg bd	x	x	N	N	N	N	
Duration depends on severity of infection, clinical response & bacteriological cultures	x	x	x	x	x	N	
Acute uncomplicated cystitis in women, treatment period 3 days	x	x	x	x	x	N	
Generally continue treatment at least 3 days after signs & symptoms of infection disappear	x	x	N	x	x	N	
Acute infections, usual duration 5 - 10 days	x	x	N	x	N	N	
Severe and complicated infections, more prolonged therapy may be required	x	x	x	N	N	x	
Streptococcal infections, treat at least 10 days	x	x	N	N	N	N	
Infections of lower respiratory tract: mild to moderate 250 - 500 mg bd, severe or complicated 750 mg bd	x	x	x	x	N	N	
Cystic fibrosis: 750 mg bd. Dose range 7.5 - 15 mg/kg/day	x	x	N	N	N	N	
Urinary tract infections: Acute, uncomplicated cystitis, 250 mg bd, mild to moderate 250 mg bd, severe or complicated 500 mg bd	x	x	x	N	x	x	
Skin infections: mild to moderate, 500 mg bd, severe or complicated 750 mg bd	x	x	x	x	x	x	
Infectious diarrhoea: 500 mg bd	x	x	x	N	x	x	
Bone infections: mild to moderate 500 mg bd, severe or complicated 750 mg bd. Treatment for 4-6 weeks or longer	x	x	x	N	x	N	
Gonorrhoea: single dose 250 mg	x	x	x	x	N	x	
Elderly: lowest possible dose	x	x	N	N	N	N	Mean of p values=Overall p value=0.92+0.42+0.38+0.46+0.21+5=0.48
Impaired renal or liver function: prolonged half life therefore adjust dosage:	x	x	x	N	x	N	
Renal insufficiency: Cr Cl ≥ 31 ml/min/1.73m2 - max 800 mg/day IV; Cr Cl ≤ 30 ml/min/1.73m2 - max 400 mg/day IV; impaired renal function & haemodialysis - as above after dialysis on dialysis days	x	mg/day orally); N	N	N	x	mg/day orally); 500	q=1-0.48=0.52
Renal impairment & CAPD: 50 mg/l of dialysate QID, or 500 mg orally or 2 x 250 mg orally	x	x	N	N	N	N	pq=0.48x0.52=0.25
CAPD patients with peritonitis: 500 mg QID orally	x	x	N	N	N	N	Std Deviation= $\sqrt{(pq+n)}=\sqrt{(0.25+5)}=\sqrt{0.05}=0.22$
Hepatic impairment: no dose adjustment	x	x	N	N	N	N	95% CI = $p \pm (2.776 \times \text{Std Dev}) = p \pm (2.776 \times 0.22) = p \pm 0.62$
Hepatic & renal impairment: as above for renal insufficiency/renal impairment	x	x	N	N	N	N	95%CI = 0.48±0.62 ie. 1.1 to -0.14
Total	24	22	10	9	11	5	
p= proportion		p=22/24=92	P=10/24=42	9/24=38	p=11/24=46	p=5/24=21	
3. CAUTIONS							
Warnings							
Use with caution in pts with history of convulsive disorders -boxed warning	x	x	N not boxed	N not boxed	N not boxed	N not boxed	
Crystalluria - pts to be well hydrated & excessive urinary alkalinity avoided boxed warning	x	x	N	N not boxed	N	N not boxed	
Treatment of Ps. Aeruginosa infections, use concomitant aminoglycoside	x	N	N	N	N	N	
Total	3	2	0	0	0	0	
p= proportion							
Pregnancy & Lactation							
Safety not established	x	x	x		x	x	
Contra-indications							
History of hypersensitivity to ciprofloxacin, any other quinolones or any of the inactive ingredients	x	x	x	x	x	x	
Pregnancy & Lactation	x	x	N	x	N	N	
Children under 18 years of age - boxed warning	x	x	N not boxed	x	N	N	
Total	4	4	2	3	1	2	
p= proportion							

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Special precautions

Impaired ability to drive motor vehicle or operate machinery, esp in combination with alcohol

Total 1 1 1 1 0 1

p= proportion

Total Cautions

8 7 3 4 2 3

p= proportion

q=1-0.48=0.52
pq=0.48x0.52=0.25
Std Deviation= $\sqrt{(pq \cdot n)} = \sqrt{(0.25 \cdot 5)} = \sqrt{0.05} = 0.22$
95% CI = $p \pm (2.776 \cdot \text{Std Dev}) = p \pm (2.776 \cdot 0.22) p \pm 0.62$
95%CI = 0.48 $\pm$ 0.62 ie. 1.1 to -0.14

4. SIDE EFFECTS

Side Effects

Nausea	x	x	x	x	N	x
Diarrhoea	x	x	x	x	x	x
Vomiting	x	x	x	x	x	x
Dyspepsia	x	x	x	x	x	x
Abdominal pain	x	x	x	x	x	x
Pseudomembranous colitis	x	x	x	x	x	x
Visual disturbances (eg diplopia, colour vision)	x	x	x	x	x	x
Tinnitus	x	x	x	x	x	x
Transient impairment of hearing esp high frequencies	x	x	x	x	N	x
Eosinophilia	x	x	x	x	x	x
Leucocytopenia	x	x	x	x	x	x
Granulocytopenia	x	x	N	x	x	x
Anaemia	x	x	x	x	x	x
Thrombocytopenia	x	x	x	x	x	x
Leucocytosis	x	x	x	x	x	x
Thrombocytosis	x	x	N	x	x	x
Haemolytic anaemia	x	x	x	x	x	x
Altered prothrombin values	x	x	x	x	x	x
Skin rashes	x	x	x	x	x	x
Urticaria	x	N	x	x	x	x
Photosensitivity (blisters, sensation of skin burning)	x	x	x	x	x	x
Erythema nodosum	x	x	x	x	x	x
Erythema exsudativum multiforme (minor)	x	x	x	x	x	x
Stevens-Johnson syndrome	x	x	x	x	x	x
Lyell's syndrome	x	x	x	x	x	x
Punctate skin haemorrhages (petechiae)	x	x	N	x	x	x
Haemorrhagic bullae & papules with signs of vascular involvement (vasculitis)	x	x	x	x	x	x
Dizziness	x	x	x	x	x	x
Headache	x	x	x	x	x	x
Tiredness	x	x	N	x	N	x
Nervousness	x	x	x	N	x	x
Agitation	x	x	x	x	x	x
Trembling	x	x	x	x	x	x
Insomnia	x	x	x	x	x	x
Peripheral paralgesia	x	x	x	x	x	x
Sweating	x	x	x	x	x	x
Unsteady gait	x	x	x	x	N	x
Convulsions	x	x	x	x	x	x
Increase in intracranial pressure	x	x	N	x	x	x
Anxiety states	x	x	N	N	x	x
Nightmares	x	x	x	x	N	x
Confusion	x	x	x	x	x	x
Hallucinations	x	x	x	x	x	x
Psychotic reactions	x	x	x	x	N	x
Depression	x	x	x	x	x	x
Joint pain	x	x	x	x	x	x
Joint swelling	x	x	N	x	x	x
General feeling of weakness	x	x	x	x	N	x
Myalgia	x	x	x	x	N	x
Tendosynovitis	x	x	N	x	x	x
Achilliotendinitis	x	x	x	x	x	x
Partial or complete rupture of achilles tendon	x	x	x	x	x	x
Tachycardia	x	x	x	x	x	x
Flushing	x	x	x	x	x	x
Migraine	x	x	x	x	x	x
Syncope	x	x	x	x	x	x
Crystalluria & haematuria	x	x	x	x	x	x
Interstitial nephritis	x	x	x	x	x	x
Transient renal impairment incl transient renal failure	x	x	x	x	x	x

Anaphylactic/anaphylactoid reactions (eg facial, vascular & laryngeal oedema, dyspnoea progressing to life-

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threatening shock	x	x	x	x	x	N	
Temporary elevations of transaminases	x	x	x	x	x	x	Mean of p values=Overall p value=0.97+0.88+0.97+0.84+0.97+5=0.93
Temporary elevations of alkaline phosphatase	x	x	x	x	x	x	
Cholestatic jaundice	x	x	x	x	x	x	q=1-0.93=0.07
Temporary increase in urea, creatinine or hyperbilirubinaemia	x	x	x	x	x	x	pq=0.93x0.07=0.07
Impaired taste and smell	x	x	x	x	x	x	Std Deviation= $\sqrt{(pq+n)}=\sqrt{(0.07*5)}=\sqrt{0.01}=0.12$
Hyperglycaemia	x	x	x	x	N	x	95% CI = $p \pm (2.776 \times \text{Std Dev}) = p \pm (2.776 \times 0.12) p \pm 0.33$
Hepatic necrosis	x	N	x	x	x	x	95%CI = 0.93±0.32 ie. 1.26 to 0.60
Superinfections with resistant bacteria or fungi with long-term or repeated use	x	x	x	x	N	N	
Total	68	66	60	66	57	66	
p= proportion		p=66/68=97	p=60/68=88	p=66/68=97	p=57/68=84	p=66/68=97	

5. DRUG INTERACTIONS

	Interactions					
Theophylline, increased plasma conc & prolonged half life	x	x	x	x	x	x
Iron	x	x	x	x	x	x
Antacids containing magnesium, aluminium, calcium, sucralfate, but not H2 receptor blockers	x	x	x	x	x	x
NSAID fenbufen, CNS stimulation & seizures	x	x	x	x	x	x
Cyclosporin, due to transient increases in serum creatinine conc.	x	x	x	x	x	x
Warfarin, due to warfarin toxicity	x	x	x	x	x	x
Glibenclamide, due to hypoglycaemia	x	x	x	x	N	x
Probenecid, due to increased ciprofloxacin serum concentrations	x	x	x	x	x	x
Metoclopramide, due to accelerated absorption of ciprofloxacin	x	x	x	x	N	x
Total	9	9	9	9	7	9
p= proportion		p=9/9=100	p=9/9=100	p=9/9=100	p=7/9=78	p=9/9=100
		Aug-00	Aug-06	May-06	Nov-05	Jan-06