SHALCIP (Ciprofloxacin Injection USP 0.2 % w/v)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SHALCIP (Ciprofloxacin Injection USP 0.2%w/v)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name of ingredients	**Quantity per 100 ml in mg**
Ciprofloxacin USP	200.0
Lactic Acid USP	82.50
Sodium Chloride USP	900.0
Disodium EDTA USP	10.0
Sodium Hydroxide USP	43.3
Hydrochloric Acid USP	0.1ml
Water for Injection USP	q.s. to 100ml

Note: United States Pharmacopoeia

3. PHARMACEUTICAL FORM

Solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Shalcip is indicated for the treatment of a wide variety of infections caused by susceptible gram-positive and gram-negative organisms including mixed infections caused by two or more organisms. It may also be used for infections caused by multi-drug resistant bacteria. The potent broad-spectrum antibacterial activity of Shalcip (including activity against Pseudomonas) combined with its excellent tissue penetration, enables Shalcip to be used alone effectively pending sensitivity results. However, to provide an effective coverage against anaerobes, it may be combined with metronidazole where presence of anaerobes is suspected. Shalcip is indicated for the treatment of the following infections caused by susceptible bacteria. Respiratory Tract Infection e.g. pneumonia, bronchopneumonia, infected pleurisy, empyema, lung abscess, infected bronchiectasis, acute exacerbation of chronic bronchitis and lung infections in patients with cystic fibrosis. Urinary Tract Infections e.g. acute and chronic pyelonephritis, prostatitis, cystitis, epididymitis and chronic, complicated or recurrent UTI. Gonorrhoea including urethral: rectal and pharyngeal gonococcal infections even those caused by resistant gonococci. E.N.T. Infections: e.g. otitis media, sinusitis, mastoiditis. Skin and Soft Tissue Infections: e.g. infected ulcers, wound infection, abscessed cellulitis, otitis externa, infected burns. Gastrointestinal Tract Infections: e.g. enteric fever, bacterial diarrhoea. Intra-Abdominal Infections: e.g. peritonitis, intra-abdominal abscess, cholangitis, cholecystitis, empyema of gall bladder. Gynaecological Infection: e.g. salpingitis, endometritis, pelvic inflammatory disease. Bone and Joint Infections: e.g. acute and chronic osteomyelitis, septic arthritis. Severe Systemic Infection e.g. septicemia, bacteremia and infections in immunocompromised patients.

4.2 Posology and method of administration

ADULTS: The dosage of intravenous Shalcip is determined on the basis of severity of infection, type of infecting organism and age, weight and renal function of the patient. Upper and lower UTI - 100-200 mg twice daily by slow IV infusion Lower RTI - 200mg (100 ml bottle) twice daily by slow IV infusion. In majority of other infections, 200 mg (100 ml bottle) should be administered by slow IV infection every 12 hrs. daily. Gonorrhoea - A single dose of 100 mg intravenously. The total daily dosage should be halved in patients with severe renal impairment (creatinine clearance 200ml/min) CHILDREN: Shalcip is usually not recommended for use in children. However, if the benefits of ciprofloxacin therapy are considered to out weigh the potential risk the dosage should be 5-10 mg/kg/day in 2 divided doses, depending on the severity of infection.

ADMINISTRATION: Shalcip infusion in 100 ml (200 mg) infusion bottle may be infused directly and should be administered by short term infusion over a period of 30-60 minutes. Shalcip infusion should not be used if it is found discoloured or contains any suspended particles.

DURATION OF TREATMENT: The duration of treatment depends upon the severity of infection, clinical response and bacteriological findings. The usual duration of therapy for acute infection is 5 to 7 days. Generally, therapy should be continued for at least 3 days after the signs and symptoms of the infection have disappeared. Initial intravenous administration : may be followed by oral Ciprofloxacin, wherever possible.

4.3 Contraindications

Ciprofloxacin Injection is contra indicated in individuals with a history of hypersensitivity to ciprofloxacin or any other quinolone derivative. Ciprofloxacin has been shown to cause arthropathy in weight bearing joints of immature animals. Though the relevance of this to man is unknown, it's use in children and adolescents is not recommended.

4.4 Special warnings and precautions for use

As ciprofloxacin may cause CNS stimulation, it should be used with caution in patients with CNS disorders such as severe cerebral arteriosclerosis or epilepsy. Patients receiving this drug should be well hydrated to prevent crystalluria. Excessive alkalinization of urine should be avoided. The dosage should be reduced in patients with renal impairment. Reproduction studies in animals at doses up to 6 times the usual daily human dose have not revealed any evidence of impaired fertility or teratogenicity due to ciprofloxacin. However information from well controlled studies in pregnant women is not available. Since ciprofloxacin causes arthropathy in immature animals, it should not be used in pregnant and nursing women.

4.5 Interaction with other medicinal products and other forms of interaction

Serum concentrations and elimination half-life of theophylline may be increased when it is used concurrently with Ciprofloxacin. It is recommended that patients be monitored for signs of theophylline

toxicity. During concurrent use, and dosage adjustments be made as appropriate. Probenecid delays the excretion of the drug.

4.6 Pregnancy and lactation

Usage in Pregnancy & Lactation: Use in Pregnancy - Shalcip should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in nursing mothers - Shalcip is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Shalcip, a decision should be made whether to discontinue nursing or to continue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Ciprofloxacin Injection is generally well tolerated. During clinical trials in a large number of patients, adverse effects related to drug occurred infrequently and were commonly reported as diarrhoea, vomiting, abdominal pain, headache, restlessness and rash. Other side-effects which have been reported very rarely include local irritation at the site of injection, thrombophlebitis, convulsions, arthralgia and increase in serum transaminase levels.

4.9 Overdose

In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The patient should be carefully observed and given supportive treatment, including monitoring of renal function. Adequate hydration must

be maintained. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

ATC Code: J01MA02

5.1 Pharmacodynamic properties

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (Cmax) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolone that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolone, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in-vitro mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may affect susceptibility to ciprofloxacin.

Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	**Susceptible**	**Resistant**
Enterobacteria	S 0.5 mg/L	R > 1 mg/L
Pseudomonas	S 0.5 mg/L	R > 1 mg/L
Acinetobacter	S 1 mg/L	R > 1 mg/L
Staphylococcus spp.1	S 1 mg/L	R > 1 mg/L
Haemophilus influenzae and Moraxella catarrhalis	S 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*	S 0.5 mg/L	R > 1 mg/L

1 Staphylococcus spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired 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.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES

Aerobic Gram-positive micro-organisms

Bacillus anthracis (1)

Aerobic Gram-negative micro-organisms

Aeromonas spp.

Brucella spp.

Citrobacter koseri

Francisella tularensis

Haemophilus ducreyi

Haemophilus influenzae*

Legionella spp.

Moraxella catarrhalis*

Neisseria meningitidis

Pasteurella spp.

Salmonella spp.*

Shigella spp. *

Vibrio spp.

Yersinia pestis

Anaerobic micro-organisms

Mobiluncus

Other micro-organisms

Chlamydia trachomatis ($)

Chlamydia pneumoniae ($)

Mycoplasma hominis ($)

Mycoplasma pneumoniae ($)

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

Aerobic Gram-positive micro-organisms

Enterococcus faecalis ($)

Staphylococcus spp. *(2)

Aerobic Gram-negative micro-organisms

Acinetobacter baumannii+

Burkholderia cepacia + *

Campylobacter spp.+ *

Citrobacter freundii*

Enterobacter aerogenes

Enterobacter cloacae *

Escherichia coli*

Klebsiella oxytoca

Klebsiella pneumoniae*

Morganella morganii*

Neisseria gonorrhoeae*

Proteus mirabilis*

Proteus vulgaris*

Providencia spp.

Pseudomonas aeruginosa*

Pseudomonas fluorescens

Serratia marcescens*

Anaerobic micro-organisms

Peptostreptococcus spp.

Propionibacterium acnes

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-positive micro-organisms

Actinomyces

Enteroccus faecium

Listeria monocytogenes

Aerobic Gram-negative micro-organisms

Stenotrophomonas maltophilia

Anaerobic micro-organisms

Excepted as listed above

Other micro-organisms

Mycoplasma genitalium

Ureaplasma urealitycum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

+ Resistance rate 50% in one or more EU countries

($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance

(1): Studies have been conducted in experimental animal infections due to inhalations of Bacillus anthracis spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on in-vitro susceptibility and on animal experimental data together with limited human data. Two-

month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax.

(2): Methicillin-resistant S. aureus very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following an intravenous infusion of ciprofloxacin 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.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (2030%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 23 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine,

prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display in-vitro antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally.

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1 -M_4)	9.5	2.6

Renal clearance is between 180300 mL/kg/h and the total body clearance is between 480600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.68.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.711.8 mg/L) for

children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.832.0 mg*h/L) and 16.5 mg*h/L (range 11.023.8 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 paediatric patients with various infections, the predicted mean half-life in children is approx. 45 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:

As reported 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 caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid, Sodium chloride, Disodium EDTA, Hydrochloric acid, Sodium Hydroxide,

Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Unless compatibility with other solutions/drugs 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/drugs that are physically or chemically unstable at the pH of the solutions (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C. Protect from sunlight. Keep out of reach of children

6.5 Nature and contents of container

SHALCIP Injection is available in a 100 ml container (FFS Polyethylene) packed in BOPP bag, then packed in a monocarton with package insert.

6.6 Special precautions for disposal and other handling

The ciprofloxacin infusion solution is compatible with Ringer solution, Ringer lactate solution, 5 % and 10 % glucose solutions, and 5 % and 10 % fructose solutions. When ciprofloxacin infusion solutions are mixed with compatible infusion solutions, for microbial reasons and light sensitivity these solutions must be administered shortly after admixture. For single use only. Any unused solution should be disposed off.

7. MARKETING AUTHORISATION HOLDER

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8. MANUFACTURER

SHALINA LABORATORIES PVT. LTD.

Manufacturing Site Address:

FRESENIUS KABI INDIA PVT. LTD.

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9. DATE OF REVISION OF TEXT

Every two years.

10. LEGAL CATERGORY

POM (Prescription Only Medicines)